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Le Sens du goût chez l'aveugle congénital

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Résumé

La vision est cruciale dans la recherche et l'identification de nourriture. Non seulement elle déclenche le réflexe céphalique de la digestion mais, combinée à l'expérience alimentaire, elle aide à raffiner nos prévisions par rapport aux aliments. En un simple clin d'œil, la vue renseigne sur la disponibilité, l'identité, la comestibilité, les saveurs, les textures et les contenus nutritionnel, calorique et toxique des aliments qui nous entourent. Étant donnée l'importance de la vue dans l'expérience gustative, il est judicieux de se poser la question suivante : Qu'arrive-t-il au goût en absence de vision? Cette thèse répond à cette question par l'étude de cette modalité chez l'aveugle de naissance grâce aux techniques de psychophysique et d'imagerie cérébrale. De plus, les conséquences gustatives de la cécité sont comparées à celles suivant la perte d'un autre sens important dans l'appréciation des aliments, soit l'odorat (anosmie). Les résultats comportementaux démontrent premièrement que l'absence de vision depuis la naissance abaisse la sensibilité gustative, reflétée par des seuils élevés de détection et d'identification des cinq goûts de base (sucré, salé, acide, amer, umami). Deuxièmement, bien que les aveugles congénitaux aient plus de facilité à identifier les odeurs comestibles par leurs narines (voie olfactive orthonasale), ceux-ci perdent leur avantage par rapport aux voyants quand ils doivent identifier ces stimuli placés sur la langue (voie olfactive rétronasale). Les résultats d'imagerie indiquent en outre que les aveugles congénitaux activent moins leur cortex gustatif primaire (insula/opercule) et leur hypothalamus par rapport aux voyants durant une tâche gustative. De plus, l'absence d'activation dans le cortex (« visuel ») occipital chez l'aveugle pointe vers le manque de plasticité intermodale en gustation. Chez les anosmiques congénitaux d'autre part, non seulement l'absence d'odorat diminue l'habileté à reconnaître les goûts mais elle abaisse également la force du signal dans les aires olfactives (ex : cortex orbitofrontal médial) durant une tâche gustative. Les résultats chez l'aveugle contrastent grandement avec les études antérieures soulignant l'amélioration de leurs sens extéroceptifs tels que l'audition, l'olfaction (orthonasale) et le toucher qui font tous intervenir la plasticité intermodale. Par ailleurs, les données chez l'anosmique concordent avec ceux de la littérature indiquant une diminution similaire de la chémosensation trigéminale, laquelle est également associée à un affaiblissement du circuit neural des saveurs. Ceci suggère que le sens du goût ne soit pas utile aux handicapés visuels pour percevoir l'environnement extérieur et ainsi

compenser leur perte de vision. De plus, bien que l'odorat participe à l'appréciation de la nourriture en bouche, sa perte n'entraîne pas de compensation sensorielle chez l'anosmique. Prises ensemble, ces données indiquent différents mécanismes d'adaptation suivant la cécité et l'anosmie. Elles soutiennent également le point de vue selon lequel la perception unifiée de goûts et de saveurs inclut non seulement les sens chimiques et le toucher mais également la vision. Considérant l'importance du goût et de l'alimentation dans la qualité de vie, ces résultats encouragent la société tout comme les professionnels de la réadaptation à faciliter l'accès à la nourriture ainsi qu'à l'enseignement culinaire chez les handicapés sensoriels.

Mots-clés : Gustation, vision, cécité, odorat, anosmie, plasticité intermodale.

Abstract

Vision is crucial for seeking and identifying food. Not only does it trigger the cephalic digestion reflex but, when combined with the experience of eating, it helps to refine expectations about foods. In a single eye blink, sight informs us about the availability, identity, palatability, flavours, textures as well as nutritional, caloric and toxic contents of foods surrounding us. Given the importance of sight in the gustatory experience, one may therefore ask the following question: What happens to gustation without vision? This thesis answers this question by studying this modality in congenitally blind subjects using psychophysical and brain imaging techniques. Additionally, the gustatory consequences of blindness are compared to those following the loss of another important modality involved in the appreciation of food, i.e. the sense of smell (anosmia). Behavioural results first show that the absence of vision from birth reduces the gustatory sensitivity, as reflected by higher detection and identification thresholds of the five basic tastes (sweet, salty, acid, bitter, umami). Second, although congenitally blind subjects are better at identifying palatable odorant stimuli through their nostrils (orthonasal olfactory route), they lose this advantage over sighted people when identifying these stimuli placed on their tongue (retronasal olfactory route). Neuroimaging results also reveal that congenitally blind subjects activate the primary gustatory cortex (insula/operculum) and the hypothalamus less compared to blindfolded sighted participants. Moreover, the absence of occipital ("visual") cortex activity in the blind points towards the lack of crossmodal plasticity in gustation. In congenitally anosmics, on the other hand, not only does the absence of smell lower the ability to recognize tastes but it also lowers the strength of the signal in olfactory areas (e.g. medial orbitofrontal cortex) during a gustatory task. The results in the blind greatly contrast with previous studies highlighting the enhancement of their exteroceptive senses such as audition, (orthonasal) olfaction and touch, all of which involve crossmodal plasticity. Moreover, data in the anosmic group are consistent with previous literature describing similar decrease of trigeminal chemosensation that is also associated with a weakening of the flavour neural network. This suggests that the sense of taste is not useful to the visually impaired to perceive their exterior environment and compensate for their lack of vision. Furthermore, although olfaction contributes to the appreciation of foods in the mouth, the lack of this modality does not drive sensory compensation in anosmic subjects. Taken

together, these data indicate different adaptation mechanisms following blindness and anosmia. They also support the view according to which the unified perception of tastes and flavours includes not only the chemical senses (taste, smell and trigeminal chemosensation) and touch but also vision. Given the importance of taste and eating experience in quality of life, these results encourage society as well as rehabilitation professionals to facilitate access to foods and culinary lessons in sensory deprived subjects.

Keywords: Gustation, vision, blindness, smell, anosmia, crossmodal plasticity.

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Liste des abréviations

ANCOVA	*Analysis of covariance*
ANOVA	*Analysis of variance*
AOB	*Accessory Olfactory Bulb*
AOS	*Accessory Olfactory System*
ASIC2a	Récepteur ionotrope sensible aux acides
ATP	Adénosine triphosphate
BA	*Brodmann Area*
BAQ	*Body Awareness Questionnaire*
BMI	*Body Mass Index*
BOLD	*Blood oxygen-level dependent* (dépendant du niveau d'oxygène sanguin)
Ca^{2+}	Ions calciques
CALHM1	Modulateur de l'homéostasie du calcium #1
CB	*Congenitally Blind*
CMER	Comité mixte d'éthique de la recherche
CNIB	*Canadian National Institute for the Blind*
CO_2	*Carbon Dioxide*
COF	Cortex orbitofrontal
COI	*Congenital Olfactory Impairment*
CRIR	Centre de Recherche Interdisciplinaire en Réadaptation
D	*Sniffin' Stick Discrimination sub-score*
DAG	Diacylglycérol
DARTEL	*Diffeomorphic Anatomical Registration Through Exponential Lie algebra*
EBA	*Extrastriate Body Area* (aire extra-striée du corps)
ENaC	Canal sodique épithélial
EPI	*Echo-Planar Image*
F	*Female*
FA	*Flip Angle*
FFA	*Fusiform Face Area* (aire fusiforme des visages)

FFQ	*Food Frequency Questionnaire*
FHP	Formule d'hydrolysat de protéines
FLAIR	*Fluid-Attenuated Inversion Recovery*
FLASH	*Fast Low Angle SHot*
fMRI	*functional Magnetic Resonance Imaging*
FNS	*Food Neophobia Scale*
FoV	*Field of View*
FWE	*Family-Wise Error*
GβδI3	Sous-unité de l'α-gustducin
GABA	Acide δ-aminobutyrique
GAD-7	*Generalized Anxiety Disorder scale – 7 items*
GMS	Glutamate monosodique
GPCRs	Récepteurs couplés à une protéine G
GPR120	Récepteur GPCR sensible aux acides gras
GPR4	Récepteur GPCR sensible aux protons
GPR40	Récepteur GPCR sensible aux acides gras
H^+	Protons d'hydrogène
HCl	*Hydrochloride acid*
HCN1 & 4	Protéine-canal activé par l'hyperpolarisation, modulé par les nucléotides cycliques et non sélectif aux cations #1 & 4
HRF	*Hemodynamic Response Function*
I	*Sniffin' Stick Identification sub-score*
IES	*Intuitive Eating Scale*
INLB	Institut Nazareth et Louis Braille
IP3	Inositol triphosphate
IRMf	Imagerie par résonance magnétique fonctionnelle
KU	*København Universitet* (Université de Copenhague)
L	*Left*
LOtv	*Lateral Occipital tactile-visual area* (aire latérale occipitale visuotactile)
M	*Male*
mGluR1	Récepteur métabotropique au glutamate #1

mGluR4	Récepteur métabotropique au glutamate #4
MNI	*Montreal Neurological Institute*
MOB	*Main Olfactory Bulb*
MoCA	*Montreal Cognitive Assessment*
mOFC	*medial Orbitofrontal Cortex*
MOS	*Main Olfactory System*
MP-RAGE	*Magnetization-Prepared Rapid Acquisition with Gradient Echo*
MR	*Magnetic Resonance*
MRI	*Magnetic Resonance Imaging*
MSG	*Monosodium Glutamate*
Na^+	Ions sodiques
NaCl	*Sodium chloride*
NC	*Normosmic Control*
NEO	*Food Neophobia Scale*
NFS	Noyau du faisceau solitaire
NMP	*Negative Mucosal Potentials*
OAS	*Odor Awareness Scale*
OD	*Oculus dexter (right eye)*
OFC	*Orbitofrontal Cortex*
Operc	*Rolandic Operculum*
OR	*Olfactory Receptor*
OS	*Oculus sinister (left eye)*
pACC	*pregenual Anterior Cingulate Cortex*
PBN	Noyau parabrachial
PHQ-9	*Patient Health Questionnaire – 9 items*
PIP2	Phosphatidylinositol 4,5-biphosphate
PKD1L3	Canal ionique semblable à la polykystose rénale 1-*like*-3
PKD2L1	Canal ionique semblable à la polykystose rénale 2-*like*-1
PLCβ2	Phospholipase C-β2
PTC	*Phenylthiocarbamide* (Phénylthiocarbamide)
R	*Right*

RNQ	Regroupement de Neuroimagerie du Québec
ROI	*Region Of Interest*
R_P	*Pearson correlation coefficient*
R_S	*Spearman correlation coefficient*
SC	Stimulus conditionné
SC	*Sighted Control*
SEM	*Standard Error of the Mean*
SN	Stimulus non-conditionné
SPM8	*Statistical Parametric Mapping 8*
T	*Sniffin' Stick Threshold sub-score*
T1R1/T1R3	Hétérodimère et récepteur spécifique à l'umami
T1R2/T1R3	Hétérodimère et récepteur spécifique au sucré
T1R3	Homodimère et récepteur au sucré
T1Rs	Récepteurs gustatifs de type I (T1R1, T1R2, T1R3)
T2R38	Récepteur gustatif à l'amertume sensible au PTC
T2Rs	Récepteurs gustatifs de type II spécifiques à l'amertume (ex : T2R38)
Tas1r1	*Taste receptor gene 1*
Tas1r2	*Taste receptor gene 2*
Tas1r3	*Taste receptor gene 3*
TASK-1	Canal potassique à deux domaines en tandem
TDI	*Sniffin' Stick Threshold-Discrimination-Identification*
TDU	*Tongue Display Unit* (appareil lingual de substitution sensorielle visuotactile)
TE	*Echo Time*
tERP	*trigeminal Event-Related Potentials*
TI	*Inverstion Time*
TR	*Repetition Time*
TRPM5	Récepteur transitoire membre potentiel de canaux activés par les Mélastatines #5
TRPs	Récepteurs transitoires membre potentiel de canaux
TSPA	Transmission sociale des préférences alimentaires
UNC	*Uncorrected*

VARSEEK	*VARiety SEEKing tendency scale*
VBM	*Voxel-Based Morphometry*
VDM	*Voxel Displacement Map*
vOICe	Système de substitution sensorielle visuoauditif (« *Oh I see* »)
VPLpc	Noyau ventral postérolatéral du thalamus
VPMpc	Noyau ventral postéromédial du thalamus
y	*years*

Le plaisir de la table est de tous les âges,
de toutes les conditions,
de tous les pays
et de tous les jours;
il peut s'associer à d'autres plaisirs,
et reste le dernier pour nous consoler de leur perte.

Jean Anthelme Brillat-Savarin[1]

[1] Aphorisme VII tiré de la *Physiologie du goût, ou Méditations de gastronomie transcendante* (1826)

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[2] Qui aime bien manger

[3] Qui vit pour manger

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Introduction

Selon le Grand Robert de la langue française, le nom « goût » et le verbe « goûter » viennent du latin « *gustus* » et « *gustare* », qui signifient « gorgée », « sentir le goût », « manger », mais aussi « preuve » et « essayer ». En anglais, les équivalents « *(to) taste* » renvoient au vieux-français « tast » ou « tâter »; soit du latin « *taxare* », i.e. « toucher » à maintes reprises en ressentant pour en estimer ou critiquer la valeur. Finalement, l'homonyme « goutter », soit écouler goutte à goutte, prend en sanskrit le même sens qu'avaler (« *gal* ») et réfère à la fuite, l'évanouissement et la disparition.

Comme le laissent déjà entrevoir ces étymologies, le système gustatif est intimement relié aux autres systèmes sensoriels, particulièrement à l'odorat et au toucher, et ce dès la périphérie. De plus et contrairement aux pensées populaires, les récepteurs gustatifs ne sont pas restreints à la langue mais sont omniprésents à l'intérieur du corps de l'animal. Ainsi, goûter implique une introspection, un rapprochement absolu qui, grâce notamment à l'expérience de sensations de faim, de satiété, de malaise ou de regain d'énergie, permettent à l'animal de porter des jugements de valence (attractif vs répulsif) puis de valeur (bon vs mauvais). Ceux-ci motiveront ou démotiveront la recherche et la sélection ultérieures de nourritures.

La vision est tout aussi importante pour goûter. Comme elle précède l'expérience gustative, elle contribue à la recherche et la sélection d'aliments et facilite grandement la préparation des repas. Qu'arrive-t-il au goût en absence de vision? Cette thèse tente de répondre à cette question grâce à l'étude du système gustatif chez les personnes sans expérience visuelle; i.e. les aveugles congénitaux. Dans la première partie de l'introduction, la neuroanatomie et la neurophysiologie du goût chez le primate et le rongeur sont présentées. Les sensations orales gustatives sont ensuite mises en contexte - la consommation alimentaire - avant d'aborder l'étonnante plasticité de ce sens chimique. Enfin, la problématique et les résultats de la thèse sont présentés dans les cinq articles du corps de cet ouvrage, lesquels sont suivis d'une discussion et d'une conclusion présentant différentes pistes de recherche.

1. NEUROANATOMIE ET NEUROPHYSIOLOGIE DU GOÛT

1.1 Système gustatif périphérique

1.1.1 Récepteurs, bourgeons et papilles

Les récepteurs gustatifs sont des cellules épithéliales spécialisées qui possèdent toutes les propriétés d'un neurone, à l'exception qu'il leur manque un axone. Ils sont dispersés partout à travers le corps humain, de la cavité orale au spermatozoïde en passant par les reins, le foie et le cerveau (section 1.1.2; Trivedi, 2012). Ceux de l'intérieur de la bouche sont organisés en bourgeons gustatifs, des structures microscopiques en forme de rosettes contenant entre 60 et 120 cellules chacune. Les cellules gustatives sont positionnées à l'apex des bourgeons de manière à ce que leurs microvillosités puissent entrer en contact direct avec les solutions via le pore gustatif.

Les bourgeons se retrouvent partout dans la cavité orale, i.e. sur la langue, le palais mou, et sur les parois du pharynx et du larynx (Breslin & Huang, 2006). Sur la langue, ils se rassemblent pour former des papilles. Comme l'illustre la figure 1, trois types de papilles gustatives se distinguent par leur morphologie:

a. **papilles fongiformes** : prenant l'aspect d'un champignon, elles sont situées aux deux-tiers antérieurs de la langue et contiennent en moyenne 4 ou 5 bourgeons.
b. **papilles foliées** : dessinées en forme de replis autour d'une glande salivaire Von Ebner, elles sont situées sur les côtés du tiers postérieur de la langue et contiennent au total une douzaine de bourgeons répartis de chaque côté du pli épithélial.
c. **papilles circumvallées** : larges et situées sur le tiers postérieur de la langue, elles contiennent une douzaine de bourgeons distribués dans la circonvolution. Au centre de la papille se trouve aussi une glande salivaire Von Ebner.

Enfin, de multiples papilles filiformes non-gustatives donnent à la langue son apparence rugueuse et favorisent la manipulation de la nourriture et/ou le traitement somatosensoriel (Breslin & Huang, 2006).

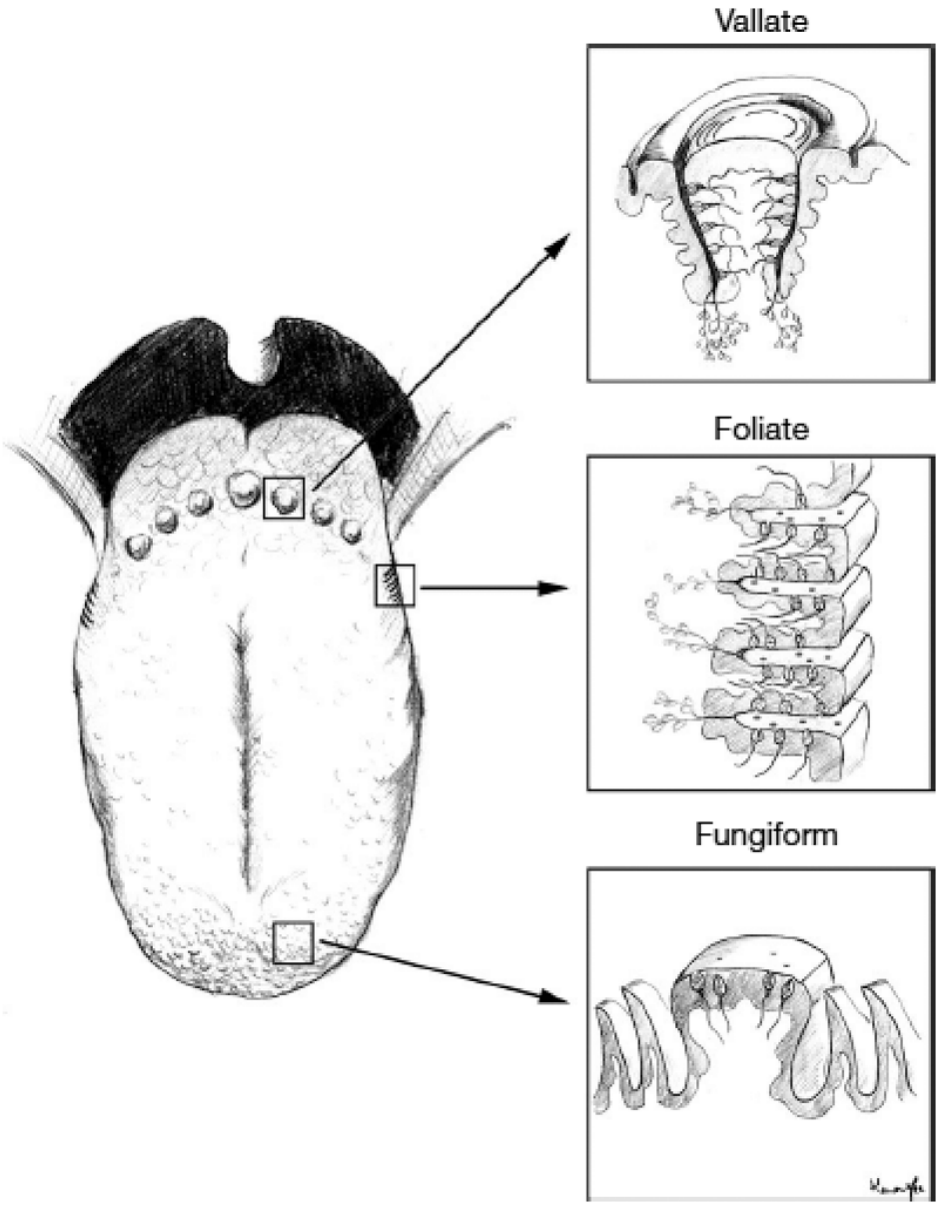

Figure 1. Les papilles gustatives vallées, foliées et fongiformes de l'Homme. Reproduit avec permission de Karger Publisher à partir de Breslin & Huang, 2006.

Lorsqu'observés par microscopie électronique, quatre types principaux de cellules gustatives se distinguent à l'intérieur des bourgeons. Les petites cellules basales rondes sont des kératinocytes qui prolifèrent à la base afin d'assurer le renouvèlement continuel des trois autres types de cellules. Les cellules de types I, II et III d'apparences sombre, claire et intermédiaire, respectivement, s'occupent de la transduction du signal gustatif. Alors que les cellules de types I (longues) et II (courtes) présentent chacune des microvillosités, seules les

cellules de type II possèdent les récepteurs gustatifs et enzymes nécessaires à la transduction, ce qui les définit pour certains chercheurs comme cellules réceptrices du goût (Breslin & Huang, 2006). Ces dernières semblent exprimer chacune les récepteurs spécifiques à un goût de sorte qu'il est possible de les diviser en cellules sucrée, salée, acide, amère ou umami (Liman *et al*., 2014). De leur côté, la plupart des cellules de type III libèrent notamment de la sérotonine et font synapses avec des neurones pseudo-unipolaires, dont les corps cellulaires se situent principalement dans les ganglions pétreux (nerf IX) et géniculés (nerf VII). La communication entre les cellules de type II et III est assurée notamment du point de vue électrique par jonctions gap et du point de vue chimique par sécrétion (autocrine et) paracrine (Breslin & Huang, 2006; Liman *et al*., 2014).

Trois nerfs crâniens innervent les bourgeons gustatifs de la cavité orale, soient les nerfs facial (VII), glossopharyngien (IX) et vague (X). Deux branches sensorielles gustatives émanent du nerf facial (VII), soient la cordée du tympan et le grand nerf superficiel pétreux. La cordée du tympan porte son nom puisqu'elle passe juste derrière le tympan dans l'oreille moyenne avant d'innerver les deux-tiers antérieurs de la langue. L'ensemble des papilles fongiformes ainsi que les papilles foliées antérieures sont innervées par cette branche. Le grand nerf superficiel pétreux innerve pour sa part les bourgeons du palais mous, presqu'aussi nombreux que sur la langue antérieure. Le nerf glossopharyngien (IX) innerve quant à lui la plupart des papilles foliées et l'ensemble des papilles circumvallées de la langue postérieure via sa branche linguale-tonsillaire. Finalement, le nerf vague innerve les bourgeons gustatifs du pharynx et du larynx via sa branche supérieure laryngée. Par ailleurs, il est important de noter qu'en plus des sensations gustatives, ces afférences sont également sensibles à la température et au toucher en plus d'être nociceptives pour la partie postérieure de la langue (Breslin & Huang, 2006).

Contrairement aux croyances populaires, la langue n'est pas cartographiée en régions spécifiques au traitement d'un seul goût particulier. Cette confusion prend origine dans la traduction anglaise erronée du travail du chercheur Allemand D.P. Hänig (1901) qui avait mesuré notamment une sensibilité au sucré plus élevée sur le bout de la langue que dans le reste de la cavité orale. En effet, il est possible de détecter le goût sucré avec n'importe quelle papille ou bourgeon gustatif. Par contre, chaque cellule gustative semble être spécifique à un goût de par les récepteurs qu'elle exprime (Liman *et al*., 2014).

1.1.2 Système chimiosensoriel diffus

Les cellules gustatives abondent également à l'extérieur de la cavité orale et sont parfois appelées « cellules chimiosensorielles solitaires », formant ensemble le « système chimiosensoriel diffus » (Sbarbati *et al*., 2010). Alors que chez l'insecte, ces cellules se retrouvent surtout à l'extérieur du corps, soit sur les pattes, les ailes, le proboscis et l'oviscapte (Liman *et al*., 2014), elles se concentrent à l'intérieur du corps chez le mammifère, i.e. dans les systèmes digestif, respiratoire, circulatoire, excréteur, reproducteur et nerveux (Deshpande *et al*., 2010; Li, 2013; Liman *et al*., 2014; Pluznick, 2013; Sbarbati *et al*., 2010). Par exemple, les cellules en brosse des intestins, des poumons et des reins sont considérées comme une sous-population des cellules chimiosensorielles solitaires. Elles expriment l'α-gustducin et sont impliquées dans la détection et le dégagement de composés chimiques de l'intérieur de la lumière (Sbarbati *et al*., 2010; Trivedi, 2012). Dans les voies aériennes, les cellules chimiosensorielles solitaires exprimant les récepteurs de l'amertume se retrouvent dans la cavité nasale et les cellules musculaires lisses. Tandis que dans le nez, elles déclenchent l'apnée pour prévenir l'inhalation d'irritants (Trivedi, 2012), elles participent à la dilatation des bronches lorsque stimulées par des substances amères (Deshpande *et al*., 2010). Les récepteurs au sucré et à l'umami (T1R1 et T1R3) sont exprimés notamment dans les spermatozoïdes (Li, 2013; Mosinger *et al*., 2013). Essentiels à la fertilité, ils permettraient de les garder dans un état stable avant leur rencontre avec l'ovule (Trivedi, 2012). Dans le système nerveux, les cellules chimiosensorielles solitaires exprimant notamment les récepteurs au sucré et à l'umami sont retrouvées à la fois dans les neurones et la glie. Elles se concentrent notamment dans l'hypothalamus, le thalamus dorsal, l'hippocampe, le cortex et le plexus choroïdien et semblent participer à la détection du glucose (Li, 2013; Ren *et al*., 2009).

Il est par ailleurs intéressant de noter que c'est dans les milieux de transition que les cellules chimiosensorielles solitaires abondent le plus. Leurs rôles exacts restent encore à confirmer, mais règle générale, elles semblent être impliquées dans les processus de sécrétion et d'absorption de même qu'à la détection d'irritants et au contrôle de la population microbienne (Sbarbati *et al*., 2010).

1.1.3 Réception et transduction

Les goûts sucré et umami (savoureux en Japonais) mesurent respectivement les contenus en glucides et en acides aminés qui signalent ensemble une teneur élevée en énergie. Ces deux goûts se partagent la famille de récepteurs gustatifs de type I, ou T1Rs, qui possèdent sept passages transmembranaires et sont couplés à une protéine G (GPCRs), l'α-gustducin. Les T1Rs se divisent en trois types : T1R1, T1R2 et T1R3 tandis que leurs trois combinaisons (les hétérodimères T1R1/T1R3 et T1R2/T1R3 ainsi que l'homodimère T1R3) donnent à la cellule gustative une sensibilité différente. Ainsi, les cellules dans lesquelles est exprimé l'hétérodimère T1R2/T1R3 sont spécifiques au sucré et peuvent être activées par tous les composés sucrés incluant sucres (ex : fructose) et acides aminés (ex : glycine) alors que les cellules T1R1/T1R3 sont spécifiques à l'umami et peuvent être activées par plusieurs acides aminés (ex : glutamate). Quant aux cellules exprimant seulement T1R3, il leur faudra des composés sucrés en plus grande concentration pour produire une réponse. Parmi les autres candidats potentiels à la réception du sucré et de l'umami se trouvent respectivement les canaux potassiques sensibles à l'adénosine triphosphate (ATP), similaires à ceux observés dans les cellules β pancréatiques (Liman *et al*., 2014; Yee *et al*., 2011), ainsi que les récepteurs métabotropiques au glutamate mGluR1 et mGluR4 (Breslin & Huang, 2006; Kusuhara *et al*., 2013).

L'amertume requiert pour sa part la famille de récepteurs gustatifs de type II, ou T2Rs, également des GPCRs. Chaque type de T2R répondrait à une sélection de substances amères de sorte que les cellules présentant une grande variété de T2Rs seraient activées par un plus grand nombre de composés chimiques. Cependant, cette spécificité accrue est contrebalancée par une plus faible sensibilité (Liman *et al*., 2014). L'Homme possède 25 gènes fonctionnels et entre 8 et 11 pseudogènes codant pour les T2Rs, ce qui en fait la plus grande famille de pseudogènes gustatifs. Des pseudogènes émergents ont également été détectés dans certaines ethnies ce qui laisse croire que la pseudogenèse des récepteurs à l'amertume est un procédé actuel reflétant probablement l'évolution de l'alimentation humaine (Breslin & Huang, 2006). Parmi ces variations génétiques rencontrées chez l'humain se trouve T2R38 qui se lie au phénylthiocarbamide (PTC), une substance très amère mais perçue comme n'ayant pas de goût par une personne sur quatre (Liman *et al*., 2014). Ce phénomène est référé comme étant « l'aveuglément à un goût », ou en anglais *blind taste*.

Bien que d'autres mécanismes de transduction semblent entrer en jeu (Li, 2013), les goûts sucré, umami et amer se partagent le même mécanisme principal de transduction du signal impliquant la cascade de l'inositol triphosphate (IP3). Une fois le récepteur GPCR activé, la sous-unité GβδI3 de l'α-gustducin se détache pour activer la phospholipase C-β2 (PLCβ2) et cliver le phosphatidylinositol 4,5-biphosphate (PIP2) en diacylglycérol (DAG) et IP3. En tant que second messager, l'IP3 se lie aux canaux calciques du réticulum endoplasmique pour provoquer l'augmentation de la concentration intracellulaire en ions calciques. Cette concentration accrue provoque à son tour l'activation des canaux ioniques TRPM5 de la membrane cellulaire. Ces derniers laissent alors entrer les ions sodiques, provoquant ainsi une dépolarisation de la cellule. Finalement, cette dépolarisation permet aux canaux modulateurs de l'homéostasie du calcium 1, CALHM1, de relâcher de l'ATP qui agira comme neurotransmetteur (Liman *et al*., 2014).

Les goûts salé et acide, parfois appelés « goûts minéraux », se distinguent des trois autres goûts « organiques » puisque leurs récepteurs sont des canaux ioniques (Liman *et al*., 2014). Le goût salé permet de détecter la présence de certains cations, en particulier les ions sodiques (Na^+), qui sont impossibles à emmagasiner chez les animaux terrestres et d'eau douce. Chez le rongeur, il existe deux types de mécanismes qui sous-tendent la sensibilité au salé et ceux-ci se distinguent par leur sensibilité à l'amiloride. Alors que le canal sodique épithélial (ENaC), une protéine hétérotétramérique retrouvée dans les reins, a été identifié comme récepteur du mécanisme sensible à l'amiloride, celui participant au second demeure encore inconnu (Breslin & Huang, 2006). Chez l'humain, seul ce deuxième mécanisme semble être impliqué dans la transduction du salé mais ses détails restent encore à être élucidés (Roper, 2007).

Le goût acide est aussi produit par des ions, ces derniers formant un « acidophore commun » (Shallenberger, 1993). Sa perception permet notamment de maintenir l'équilibre acido-basique essentiel à l'homéostasie. Des études psychophysiques chez l'humain (revue dans Roper, 2007) suggèrent que les ions en jeu incluent à la fois les protons hydrogène (H^+; surtout pour les acides inorganiques comme l'acide chlorhydrique) et les anions d'acides organiques (ex : acide citrique) pouvant traverser la membrane cellulaire. Parmi les candidats des récepteurs à l'acide se trouvent le récepteur ionotrope sensible aux acides ASIC2a, les

protéines-canaux HCN1 et HCN4, le récepteur GPCR sensible aux protons GPR4, les récepteurs ionotropes PKD2L1 et PKD1L3 de la famille des TRPs ainsi que le canal potassique à deux domaines en tandem TASK-1. Cependant, alors que les recherches semblent se concentrer sur les récepteurs aux acides extracellulaires, il semblerait que ce soit l'acidification intracellulaire qui déclenche la transduction (Roper, 2007). Plus de travaux seront donc nécessaires pour élucider les processus de réception et de transduction du goût acide.

Hormis ces cinq goûts canoniques, certains chercheurs suggèrent d'ajouter le gras, l'eau ou encore le calcium comme goûts de base. La découverte des récepteurs couplés à une protéine G, les GPR40 et GPR120, spécifiques aux acides gras et exprimés dans les cellules gustatives humaines supportent l'idée que le gras ne soit pas seulement perçu par le toucher et l'odorat (Liman *et al*., 2014). En ce qui concerne le goût du calcium, celui-ci impliquerait la sous-unité commune au sucré et à l'umami, T1R3, qui agirait comme un détecteur aversif. Finalement, alors que l'habileté à détecter l'eau présente de clairs avantages pour maintenir la balance osmotique (Gilbertson *et al*., 2006), aucun récepteur ne lui a encore été associé (Liman *et al*., 2014).

Fait intéressant, certaines nourritures peuvent influer sur la réception et la transduction du signal gustatif. C'est le cas de certaines plantes exotiques dont la miraculine (*Synsepalum dulcificum*), le ziziphine (*Ziziphus jujuba*) et la curculine (*Curculigo latifolia*) ainsi que des extraits de fèves ou d'ail (contenant des produits de dégradation protéolytiques de protéines, tels que le δ-L-glutamyl-L-leucine). La miraculine est tirée de la baie miracle rouge Africaine et transforme les goûts acide et amer en sucré tandis que la curculine (ou néoculine) provient de la Malaisie et donne un goût sucré à l'eau (Kurimoto *et al*., 2007). Pour sa part, le ziziphine supprime le goût sucré sans affecter pour autant les quatre autres goûts de base (Smith & Halpern, 1983). Bien que leurs mécanismes d'action restent encore à élucider, il est possible que ces illusions soient produites en interagissant avec les récepteurs gustatifs, tel que démontré pour la curculine et l'hétérodimère T1R2/T1R3 par Kurimoto *et al*. (2007). Finalement certains extraits d'ail et de fèves légèrement astringents lorsque consommés individuellement viennent rehausser la complexité et le caractère délicieux des goûts umami,

salé et sucré lorsqu'ils sont ajoutés à de tels aliments (Dunkel *et al*., 2007). Ces substances modulatrices dites « kokumi » impliquent les récepteurs sensibles au calcium (Maruyama *et al*., 2012).

1.1.4 Codage du signal

Suivant la transduction, le signal est ensuite transmis au système gustatif central via les trois nerfs crâniens. Ce signal est codé dans le système nerveux périphérique selon deux principaux modèles. Le premier propose un codage par étiquetage (ou *labelled line* en anglais), i.e. à chaque cellule gustative correspond un neurone spécifique. Dans ce modèle, l'identité du goût se fait par stimulation de la cellule gustative puisqu'il n'y a pas de chevauchement ultérieur entre les goûts. Le deuxième modèle propose un codage distributif, similaire au codage d'odeurs dans le bulbe olfactif. Ce dernier suggère que chaque cellule réceptrice ou chaque neurone afférent réponde de façon différente aux cinq goûts de base et que l'identification des goûts se fasse ultérieurement dans le système nerveux central (Chandrashekar *et al*., 2006; Liman *et al*., 2014). Certains chercheurs ont aussi proposé un modèle de codage par étiquetage lié aux valences comportementales de rejet ou d'acceptation (Liman *et al.*, 2014). Bien que ces théories soient encore discutées, les preuves soutenant le codage par étiquetage abondent davantage (Huang *et al*., 2006), ce qui a permis à Zuker et son équipe de suggérer qu'il existe, analogiquement à l'organisation rétinotopique, une « cartographie gustotopique » des informations gustatives sur le cortex, du moins chez le rongeur (Chen *et al*., 2011).

1.2 Système gustatif central

Les nerfs crâniens VII, IX et X qui convoient non seulement les informations gustatives de la cavité orale mais aussi les informations viscérales, projettent ipsilatéralement vers le noyau du faisceau solitaire (NFS) de la médulla où ils font synapses. Des études chez le rongeur (revue dans Sewards, 2004) ont démontré qu'il est possible de subdiviser le système gustatif en trois voies parallèles dès ce premier relais :

- la **voie sensorielle** codant les qualités sensorielles des stimuli gustatifs telles que leur nature et leur intensité (ou concentration);

- la **voie hédonique**, résultat d'un chevauchement entre les voies sensorielle et viscérale, intégrant autant le plaisir ou le déplaisir évoqué par les stimuli gustatifs que leurs conséquences viscérales;
- la **voie viscérale** codant exclusivement les conséquences induites par l'ingestion d'aliments tel que le gain en énergie ou les crampes abdominales.

Comme l'illustre le schéma de la figure 2, le NFS se subdivise en trois régions selon les informations sensorielles (NFS rostral), hédoniques (NFS intermédiaire) et viscérales (noyau gélatineux du NFS) qu'il traite. Alors que le deuxième relais du système gustatif chez le rat est le noyau parabrachial (PBN) du pont de Varole, chez l'humain les afférences du NFS projettent directement vers le prochain centre, soit le noyau ventral postéromédial du thalamus (VPMpc; Sewards, 2004; Simon *et al*., 2006; Topolovec *et al*., 2004). Le PBN et le VPMpc se divisent eux aussi en régions spécialisées. Alors qu'elles se chevauchent dans le PBN, la ségrégation est plus nette au niveau du VPMpc où la partie dorsolatérale traite de l'aspect sensoriel alors que la section ventromédiale se spécialise dans l'aspect hédonique. Le noyau ventral postérolatéral du thalamus (VPLpc) s'occupe pour sa part du traitement des informations viscérales.

Au niveau cortical, les afférences thalamiques gustatives projettent ipsilatéralement vers le cortex gustatif primaire, situé dans l'insula et les opercules frontale et Rolandique qui la recouvrent, puis vers le cortex gustatif secondaire, localisé dans le cortex orbitofrontal (COF). Ces deux régions entretiennent des connections importantes avec les structures limbiques, telles que l'amygdale, l'hippocampe et le cortex cingulaire. Leurs structures et fonctions sont décrites en détails ci-après.

1.2.1 Insula/Opercule

L'insula, aussi appelée « l'île de Reil », est enfouie dans la fissure sylvienne et prend le nom du scientifique qui l'a décrite en 1809 (Shelley & Trimble, 2004). Hyperdéveloppée et possédant jusqu'à 20 sulci chez les cétacés, elle est complètement lisse chez les singes du nouveau-monde et ne possède qu'un seul sillon chez les singes de l'ancien-monde. L'humain

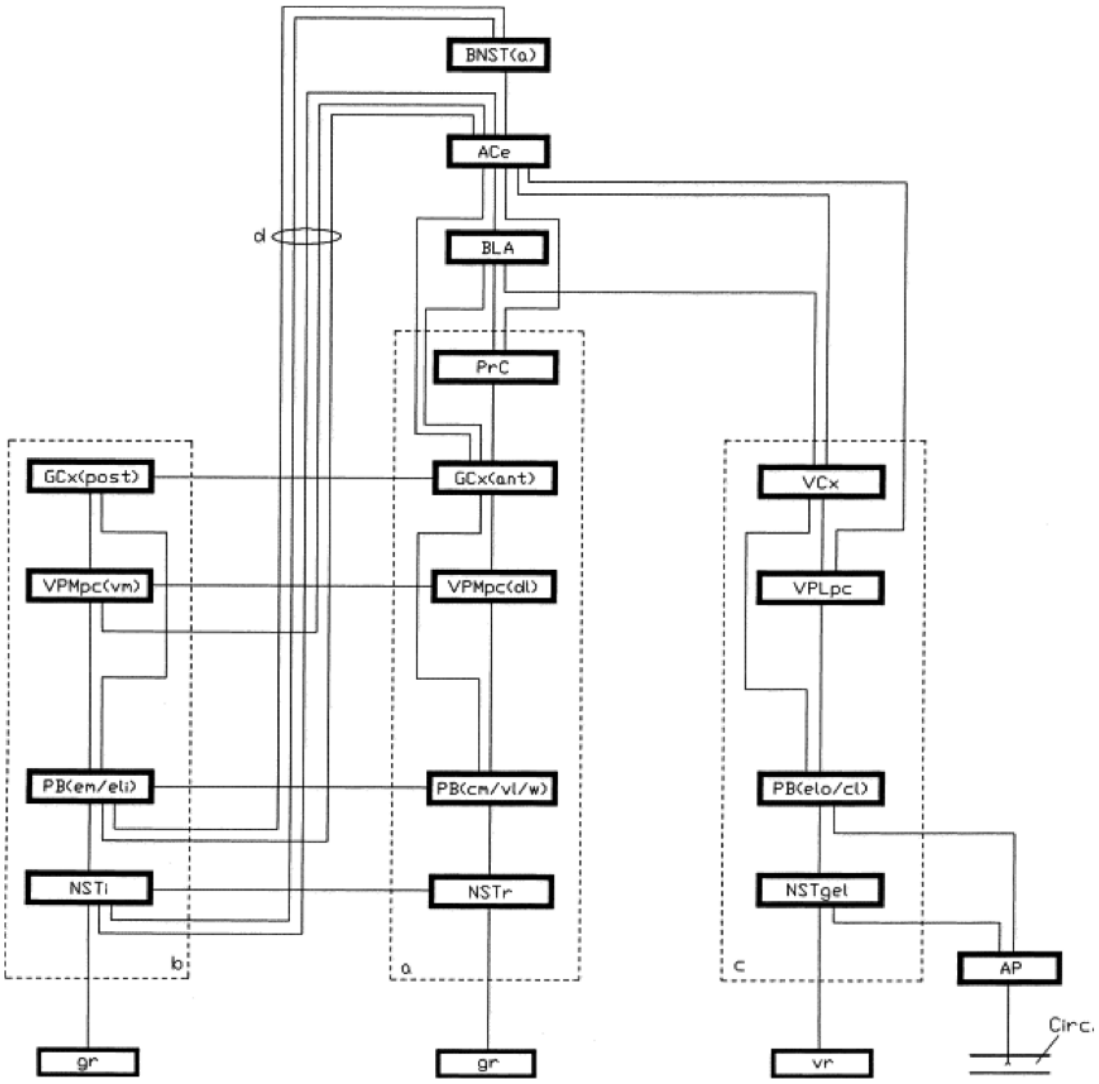

Figure 2. **Schéma du système gustatif du rat montrant les voies sensorielle (a), hédonique (b) et viscérale (c).** Abréviations : d, projections rétrogrades de l'amygdale vers les représentations hédoniques du NST; gr; récepteurs gustatifs; vr, récepteurs viscéraux; AP, area postrema; Circ, circulation sanguine; NSTi, partie intermédiaire du noyau du faisceau solitaire (NST); NSTr partie rostrale du NST; NSTgel, sous-noyau gélatineux du NST; PBcm/vl/w, parties centromédiale, ventrolatérale et sous-noyau de la taille du complexe parabrachial (PB); PBem/eli, parties extéromédiale et intérieure du sous-noyau latéral externe du PB; PBelo/cl, parties extérieure des sous-noyaux latéraux externe et central du PB; VPMpc(vm) partie ventromédiale du noyau parvicellulaire postéromédial thalamique (VPMpc); VPMpc(dl), partie dorsolatérale du VPMpc; GCx(post), cortex gustatif (GC) postérieur (hédonique); GCx(ant) GC insulaire antérieur (sensoriel); VCx, cortex viscéral insulaire; PrC, cortex périrhinal; BLA, noyau basolatéral de l'amygdale; ACe, noyau central de l'amygdale; BNST(a), division antérieure du noyau de la strie terminale. Reproduit avec permission de Elsevier à partir de Sewards, 2004.

est muni d'une insula de 5 à 7 sulci en forme de pyramide inversée. L'insula antérieure, qui comprend trois courts gyri (antérieur, moyen et postérieur) et parfois un gyrus accessoire, est exclusivement connectée au lobe frontal et reçoit notamment les informations gustatives et olfactives. L'insula postérieure munie de deux longs gyri (antérieur et postérieur) entretient des connections avec les lobes pariétal et temporal qui lui transmettent entre autres les informations auditives, vestibulaires et somesthésiques. L'île de Reil se subdivise également en trois zones cytoarchitectoniques: dorscaudale granulaire (aire de Brodmann 13) recevant les afférences sensorielles thalamiques, dysgranulaire ou de transition et antéroventral agranulaire (aires de Brodmann 14 à 16) (Shelley & Trimble, 2004).

Les connections insulaires sont extrêmement nombreuses et atteignent presque tout le cerveau, dont les noyaux de la base, le striatum, le thalamus dorsal, le cortex, l'amygdale et d'autres régions limbiques et paralimbiques. Parmi ces dernières se trouvent notamment de larges neurones bipolaires hautement myélinisés appelés Von Economo qui relient les cortex frontoinsulaire et cingulaire aux autres régions du cerveau. Véritables autoroutes d'informations, ces neurones semblent être impliqués dans l'empathie, le contrôle de soi, la conscience sociale et l'intuition (Allman *et al*., 2011; Craig, 2009). Ces nombreuses connections confèrent à l'insula des rôles multisensoriel et intégratif autant dans les processus sensorimoteurs (gustation, olfaction, toucher, audition/vestibulaire, homéostasie, douleur, expression, langage), socioaffectifs (empathie, phobie, anxiété, amour/dégout) que cognitifs associatifs (Kurth *et al*., 2010; Shelley & Trimble, 2004). Alors que l'insula postérieure renseigne sur l'état physiologique du corps offrant ainsi une représentation intéroceptive (Craig, 2003), sa section antérieure a été proposée comme le substrat de la conscience humaine (Craig, 2009). Ceci permet donc à l'Homme de faire le pont entre les évènements du monde extérieur et les divers états de son milieu intérieur (Shelley & Trimble, 2004).

Les pathologies impliquant l'insula sont nombreuses et incluent les aphasies, apraxie du langage (difficultés à articuler), dysarthries (troubles cardiaques), somatoparaphrénies, apathies, asymbolie à la douleur (perte de l'aspect désagréable de la douleur), anergie (fatigue et baisse de l'activité physique), phobies, troubles de l'anxiété, dépression, autisme, schizophrénie et démences (Shelley & Trimble, 2004). C'est sans surprise que plusieurs d'entre elles sont également caractérisées par des désordres chimiosensoriels (Amsterdam *et al.*, 1987; Heath *et al.*, 2006; Horder *et al*., 2010; Tsuichihashi *et al*., 2012).

En gustation, le cortex insulaire se spécialise notamment dans le codage de la qualité et de l'intensité des goûts (Shelley & Trimble, 2004). Les patients droitiers lésés à l'insula droite présentent des troubles d'identification et de codage d'intensité des goûts seulement lorsque stimulés sur la moitié droite de la langue. À l'opposé, les patients droitiers lésés du côté gauche ont de la difficulté à identifier les goûts stimulant les deux côtés de la langue alors que leurs troubles du codage d'intensité sont restreints à l'hémilangue gauche, suggérant que les informations gustatives croisent la ligne médiane à ce niveau (Pritchard *et al*., 1999). Chez le rat, une lésion à l'insula antérieure provoque un déficit dans l'apprentissage conditionné de goûts (ex : sucré) et de saveurs (ex : sucré + odeur d'amande) aversifs, qui survient lorsque l'animal se désintéresse des stimuli gustatifs (ex : sucré) ou olfactifs (ex : odeur d'amande) plaisants préalablement consommés et associés à un malaise (Lasiter *et al*., 1985). En tant que cortex associatif, l'insula joue donc un rôle clef dans l'intégration des saveurs, i.e. les combinaisons de goûts, odeurs et chémosensations trigéminales (De Araujo *et al*., 2003; McCabe & Rolls, 2007; revue dans Small & Prescott, 2005) mais aussi de leurs conséquences viscérales, telles que les sensations de distension de l'œsophage, brûlures d'estomac, gargouillement du tractus gastro-intestinal, nausées et dégout ainsi que les réponses de mastication, salivation, vomissement et défécation (Shelley & Trimble, 2004).

En résumé, contrairement aux cortex visuel et auditif primaires qui sont presque exclusivement dédiés au traitement d'une modalité, le cortex gustatif primaire est hautement multimodal et cognitif.

1.2.2 Cortex orbitofrontal

Les afférences gustatives insulaires projettent ensuite vers le cortex orbitofrontal (COF, anatomiquement désigné « cortex orbital et médial préfrontal »; Price, 2007), considéré comme le cortex gustatif secondaire. Hyperdéveloppé chez l'humain, il contient aussi des sections granulaire (deux tiers rostral), dysgranulaire et agranulaire (tiers caudal), chacune connectée avec leur homologue insulaire. Il est possible de subdiviser ce cortex en vingt-trois zones selon leurs architectonie, connections et fonctions (Price, 2007). Ces dernières peuvent se regrouper en deux circuits interreliés, soient orbital et médial. Le circuit orbital reçoit les afférences sensorielles gustatives, olfactives, tactiles et visuelles de la voie ventrale et est également connecté aux aires multisensorielles dans les cortex préfrontal ventrolatéral et

périrhinal. Il se spécialise dans l'intégration des objets sensoriels comme les aliments. Pour sa part, le circuit médial projette vers l'hypothalamus, le tronc cérébral, le cortex dorsomédial préfrontal, le parahippocampe et est impliqué notamment dans la régulation des émotions, de l'humeur (Price, 2007) ainsi que le contrôle de la prise de nourriture (Rolls, 2008).

L'encodage des plaisirs et des récompenses suivent respectivement les axes médiolatéral et antéropostérieur du COF. Les stimuli plaisants comme le sucré sont codés préférablement dans le COF médial alors que les stimuli déplaisants tels que l'amertume activent davantage le COF latéral (Berridge & Kringelbach, 2013). Les récompenses simples telles que la nourriture sont traitées dans le COF antérieur alors que les récompenses plus complexes comme l'argent sont encodées dans la région postérieure (Gottfried & Zelano, 2011).

Les fonctions de ce cortex hautement cognitif se résument à « encoder, assigner, mettre à jour, intégrer, surveiller, comparer et/ou calculer les valeurs subjectives et hédoniques d'une récompense, d'un stimulus ou d'une action » (Gottfried & Zelano, 2011). Les lésions au COF perturbent la prise de décision basée sur les valeurs subjectives, telles que le choix de manger certaines nourritures et d'en rejeter d'autres (revue dans Padoa-Schioppa & Cai, 2011). De plus, le recrutement du COF suite aux stimulations gustatives est dépendant du niveau de faim et de soif du sujet, ces derniers ajustant la valeur de récompense que représente une nourriture ou une boisson (Critchley & Rolls, 1996; Rolls, 1997). Comme l'humain a intérêt à varier sa diète pour puiser les différents nutriments dont il a besoin, la sensation de satiété peut être spécifique à une nourriture. Ceci se produit quand un aliment est mangé (ou même seulement senti) sur une période de 10 à 15 minutes et que son évaluation hédonique décroit au fur et à mesure sans affecter les évaluations hédoniques des aliments auxquels le sujet n'est pas exposé (Rolls, 2011). Le terme de satiété sensorielle-spécifique est utilisé pour décrire ce phénomène sous-tendu par le COF (Rolls, 1997; 2008; 2011). L'ablation du COF diminue cet effet de satiété sur la consommation alimentaire (Padoa-Schioppa & Cai, 2011). De plus, une lésion droite au COF latéral diminue les habiletés olfactives (Zatorre & Jones-Gotman, 1991; Li *et al*., 2010) en plus d'éliminer toute conscience olfactive (Li *et al*., 2010).

En raison des caractères hautement intégratif, multisensoriel et cognitif des cortex gustatifs primaire et secondaire, il n'est pas surprenant que le goût soit sujet à une forte plasticité. Toutefois, avant d'aborder ce sujet, il est important de placer la gustation dans son

contexte, à savoir la consommation alimentaire. Ceci aidera à mieux comprendre les plasticités intra- et intermodale du système gustatif.

2. CONSOMMATION ALIMENTAIRE

2.1 Exploration vs exploitation

Alors que la vue, l'ouïe, l'odorat et - jusqu'à un certain point - le toucher sont constamment bombardés de stimuli provenant de l'environnement extérieur, la stimulation de la langue cachée dans la cavité orale est surtout basée sur un processus décisionnel complexe, i.e. la consommation alimentaire. Pour consommer, l'individu doit d'abord répondre, consciemment ou inconsciemment, à une série de questions critiques incluant: Où trouver la nourriture? Quel(s) aliment(s) sélectionner? Quelle quantité ingurgiter? À quel(s) moment(s) et à quel(s) endroit(s) manger? (Begg & Woods, 2013). L'ensemble de ces réponses a pour but ultime le maintien de l'homéostasie tout en favorisant l'expérience de plaisirs.

Chez l'homme comme chez l'animal, l'organisme fait alors face à un problème économique classique : l'optimisation du comportement afin que le temps d'exploration (ex : essai de nouvelle nourriture de valeur nutritive inconnue) soit balancé avec celui d'exploitation (ex : consommation de nourriture familière) (Kringelbach & Stein, 2010). Alors que les stratégies d'exploration visent à satisfaire le désir de trouver une nouvelle source alimentaire riche en nutriments, celles relevant de l'exploitation assurent la préservation de la vie. Le circuit de la récompense occupe une place centrale pour assurer cet équilibre puisqu'il permet d'analyser à la fois la saillie incitative (« je veux ») et l'impact hédonique (« j'aime ») de la nourriture.

2.2 Manger avec les yeux

En tant que sens téléréceptif par excellence, la vision atteint les objets les plus éloignés, distants jusqu'à l'horizon. De plus, elle saisit simultanément une multitude d'informations en un seul clin d'œil. Ces qualités lui confèrent un rôle crucial dans la consommation alimentaire en guidant la recherche de nourriture (voie dorsale) mais aussi en facilitant la reconnaissance

d'aliments (voie ventrale). Enfin, la vision informe aussi sur le contexte environnemental dans lequel la consommation a intérêt à être recherchée ou évitée.

Comme les comportements d'exploration présentent certains risques (ex : dépense d'énergie sans absorption suffisante de nutriments), le cerveau a intérêt à simuler les conséquences de l'absorption de divers aliments afin de mieux les comparer. L'organisme est donc entrainé à inférer hâtivement les caractéristiques multisensorielles (ex : goût, saveurs, texture), nutritives et hédoniques (ex : plaisir, déplaisir) des aliments afin d'optimiser le comportement. La vision donne accès à une multitude d'informations précieuses qui permettent, à travers l'expérience ancrée dans la mémoire, de raffiner ces inférences.

Au niveau cérébral, ces inférences sont reflétées par l'activation du système gustatif à la simple vue d'un aliment, soit bien avant sa mise en bouche. Par exemple, en plus des zones impliquées dans le plaisir et la faim, la lecture des plats figurant sur un menu de restaurant (vs mots incomestibles) ou la vue d'un gâteau au chocolat (vs un objet incomestible) active les aires gustatives primaires et secondaires (Barros-Locertales *et al*., 2011; revue dans Van der Laan *et al*., 2011). Cet amorçage a aussi l'avantage de préparer le corps à l'absorption de nourriture en déclenchant par exemple la salivation, la sécrétion de sucs gastriques et d'hormones (Crum *et al*., 2011; Feldman & Richardson, 1986; Powley, 2000), qui contribuent en retour à accélérer la prise de décision (Powley, 2000).

Au niveau comportemental, si l'expérience interne suivant la première bouchée correspond assez bien aux attentes, une réponse d'assimilation est observée. Cependant, si la différence entre les attentes et l'expérience interne est trop grande, une réponse de contraste survient (Shankar *et al.,* 2010; Wilson *et al.,* 1989). Par exemple, étiqueter une crème glacée rose au saumon fumé avec les termes « crème-glacée » ou « mousse [umami] savoureuse » produit deux réponses opposées (rejet vs acceptation) du même aliment en fonction de la précision de l'étiquetage (Yeomans *et al.*, 2008).

2.3 Sentir et toucher pour mieux savourer

L'odorat parvient également à guider vers une source de nourriture, bien que ces habiletés soient plus évidentes chez l'animal et le petit enfant allaité (Porter *et al*., 2007; Varendi & Porter, 2001). Sentir des odeurs attire l'attention visuelle vers les objets congruents

(Durand *et al*., 2013; Seo *et al*., 2011). L'Homme réussit également à identifier sa nourriture en se basant seulement sur des indices olfactifs. Cependant, cette capacité est assez restreinte et la majorité des informations olfactives est traitée de manière subconsciente et en parallèle avec d'autres stimuli sensoriels (Köster *et al*., 2014). Après avoir vu un aliment intéressant, l'action suivante est souvent sa préhension puis son reniflement via la voie olfactive orthonasale pour en vérifier sa comestibilité. Le rôle principal de l'odorat comme du toucher dans la consommation est d'évaluer (ou confirmer) non seulement la (in)comestibilité mais également le plaisir suscité par un aliment. Enfin, puisque la nourriture est rarement associée qu'à de simples goûts de base, ces deux sens participent étroitement à la perception riche et diversifiée de saveurs suivant la mise en bouche.

Ensemble, le mélange de goût(s), d'odeur(s) et/ou de texture(s)/ température(s)/ chémosensation(s) trigéminale(s) composent les saveurs (Small & Prescott, 2005). Une saveur de mojito possède donc des goûts sucré et acide, des odeurs de lime et de menthe, une température glacée, une texture liquide ainsi que des chémosensations trigéminales de fraicheur et d'astringence. Lors de leur mise en bouche, la nourriture et les boissons stimulent en plus des récepteurs gustatifs les récepteurs somesthésiques de la branche mandibulaire (V3) du nerf trigéminal de la cavité orale. Libérées durant la mastication et conviées à la cavité nasale durant l'expiration (voie olfactive rétronasale; Bojanowski & Hummel, 2012), les molécules odorantes activent en parallèle l'épithélium olfactif (nerf crânien I) et les récepteurs somesthésiques des branches ophtalmique (V1) et maxillaire (V2) du nerf trigéminal. L'illusion de localisation des odeurs référées à la bouche plutôt qu'au nez engendre une confusion d'apparence synesthésique courante chez les gens qui considèrent à tort les odeurs rétronasales comme des goûts. L'expression « je ne goûte plus rien » employée pour décrire la perception diminuée des saveurs des aliments consommés lors d'une congestion nasale devrait donc être corrigée par « je ne savoure/sens plus rien ».

Le système gustatif interagit donc avec les systèmes olfactif et somatosensoriel /trigéminal pour engendrer la perception unifiée de saveurs. Le lecteur intéressé dans l'anatomie de ces systèmes est invité à consulter les articles de revue suivants : systèmes olfactif (Benignus & Prah, 1982; Patel & Pinto, 2014) et somesthésique (Upadhyay *et al*., 2008; Schnitzler & Ploner, 2000; Sewards & Sewards, 2002). Chez l'humain, ces trois sens convergent dans le système nerveux central aux niveaux des cortex gustatifs primaire (insula)

et secondaire (COF) où la perception unifiée des saveurs est créée (revue dans Small *et al*., 2013). Par ailleurs, l'insula a été proposée par Craig (2002) comme cortex primaire du système intéroceptif, aussi appelé système spinothalamocortical de la lame I, qui traite de la thermoréception, viscéroception et de la douleur, alors que les cortex insulaire et orbitofrontal représentent des cortex olfactifs d'ordre supérieur. La figure 3 ci-après présente un résumé des systèmes impliqués lors de la prise alimentaire.

3. PLASTICITÉ DU SYSTÈME GUSTATIF

Le système gustatif possède une très forte plasticité qui interagit avec l'expérience individuelle pour modeler les préférences alimentaires (Mennela, 2014). Le développement des préférences alimentaires est perpétuel tout au cours de la vie puisqu'il s'ajuste notamment aux besoins changeants de l'organisme. Les réponses hédoniques aux stimuli gustatifs sont donc intrinsèquement plastiques, alors que les réponses qualitatives ne le sont pas (Spector & Travers, 2005). Les facteurs qui régissent la plasticité du système gustatif sont liés à l'exposition aux milieux intérieur et extérieur, dont le premier est modifiable par la diète.

3.0.1 Ontogénèse des préférences alimentaires

Dès la gestation, le système gustatif de l'enfant à naître est exposé, via le liquide amniotique, aux molécules volatiles que sa mère ingère et respire. Suivant la naissance, ces mêmes molécules sont présentes dans le lait maternel offrant à l'enfant un continuum de saveurs propres à la consommation. Ce continuum a l'avantage de faciliter le sevrage de l'enfant puisque ce dernier reconnait les composés auxquels il était exposé par les fluides maternels dans la diète de sa famille. Ceci se reflète par la préférence des enfants sevrés envers les légumes consommés par leur mère durant la grossesse ou l'allaitement (Mennella & Ventura, 2011).

La prédilection innée pour le sucré et l'aversion naturelle à l'amertume se détectent dès la vie fœtale. Si des composés sucrés sont injectés dans le liquide amniotique, le fœtus augmente sa fréquence de déglutition alors qu'il la décroît pour l'addition de composés amers (Mennella & Ventura, 2011). Cette observation s'étend chez les prématurés qui, entre 33 et 40

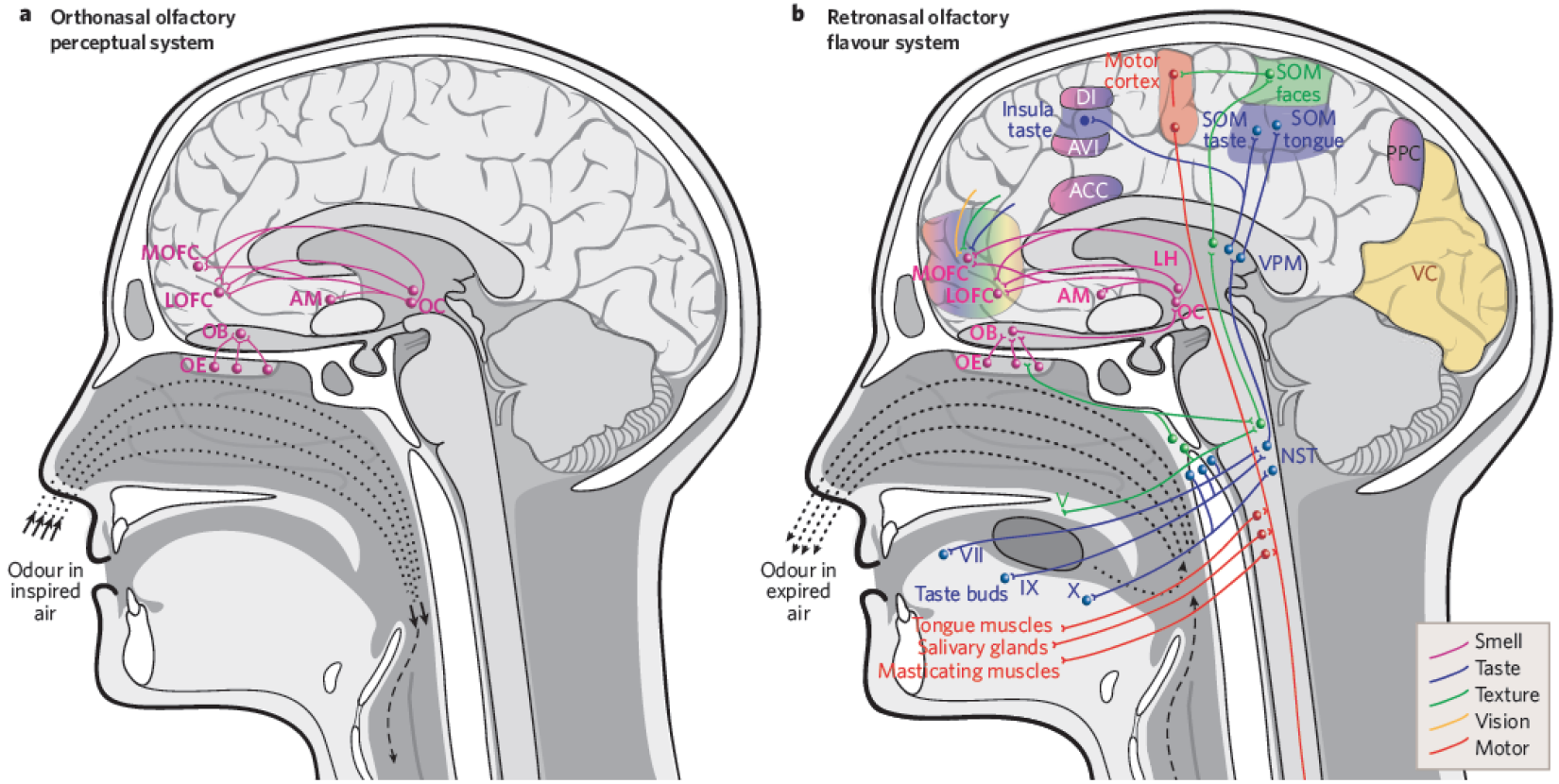

Figure 3. Les systèmes olfactifs orthonasal (a) et rétronasal (b), dont le dernier fait partie intégrante du circuit des saveurs. ACC, noyau accumbens; AM, amygdale; AVI, cortex insulaire antéroventral; DI, cortex insulaire dorsal; LH, hypothalamus latéral; LOFC, cortex orbitofrontal latéral; MOFC, cortex orbitofrontal médial; NST, noyau du faisceau solitaire; OB, bulb olfactif; OC, cortex olfactif; OE, épithélium olfactif; PPC, cortex pariétal postérieur; SOM, cortex somatosensoriel; V, VII, IX, X, nerfs crâniens; VC, cortex primaire visuel; VPM, noyau thalamique ventral postéromédial. Reproduit avec permission de Nature Publishing Group à partir de Shepherd, 2006.

semaines suivant la conception, augmentent ou diminuent leur fréquence de succion sur des tétines de latex imbibées de solutions sucrées ou amères (Mennella, 2014). Chez le primate nouveau-né, les réponses gusto-faciales de sourires ou de grimaces sont exprimées suite à l'exposition aux goûts sucré et amer, respectivement (Steiner *et al*., 2001). Ces réponses relèvent de réflexes puisqu'elles sont aussi présentes chez les enfants anencéphales (Steiner, 1973).

Le penchant envers le salé est aussi affecté par l'expérience fœtale. Les enfants nés de mères souffrant de sévères nausées matinales mangent plus d'aliments salés, de l'âge de 4 mois jusqu'à l'adolescence et même durant leur vie adulte. Similairement, les individus ayant souffert eux-mêmes de diarrhée ou de vomissements durant leur enfance préfèrent les aliments à forte teneur en sel (Mennella, 2014). Cette préférence est aussi marquée chez les sportifs qui perturbent leur équilibre osmotique régulièrement et ont besoin d'apports en eau comme en sels pour le rétablir (Leshem *et al*., 1999; Wald & Leshem, 2003).

3.0.2 Périodes critiques

Naturellement, les enfants nourris de laits infantiles aux saveurs monotones ne sont pas exposés aussi longtemps à la même diversité de composés que ceux nourris au sein. L'utilisation de laits infantiles a par contre l'avantage de fournir aux chercheurs un moyen contrôlé pour l'étude des périodes critiques du développement des préférences alimentaires. Les travaux de Beauchamp et Mennella (2011) ont notamment démontré que c'est avant l'âge de 4 mois que l'enfant manifeste sa plus grande acceptation aux nouveaux goûts. Les enfants de moins de 4 mois exposés à une formule d'hydrolysat de protéines (FHP) qui possède un goût très désagréable, acceptent cette nourriture alors que les plus âgés la rejettent. Comme les FHP sont dotées de sulfures et d'acides aminés qui possèdent des goûts prononcés d'amertume et d'umami, les enfants nourris par ces formules mangent davantage les céréales et les légumes dotés de ces saveurs, tels que les crucifères. Leur préférence est également proportionnelle à la durée de l'exposition aux FHP (Mennella, 2014). Comme l'argumentent les auteurs, cette période sensible de quatre mois donne les effets les plus permanents mais n'est pas en soi une « période critique » en dehors de laquelle tout développement des préférences alimentaire est impossible. La plasticité est plutôt inhérente à la voie hédonique du système gustatif tout au cours de la vie.

La présence d'une plasticité gustative révélée non tant par l'âge de l'animal mais par ses besoins suggère une autre définition du terme « période critique ». Une récente étude portant sur la plasticité du système visuel par Spolidoro et collègues (2011) soutient ce point de vue. Lorsque privés de stimulation visuelle dans un œil durant une semaine, les rats adultes ne montrent pas de changement plastique au niveau cortical à moins qu'ils aient été privés de nourriture un jour sur deux (Spolidoro *et al*., 2011). Similairement, les rats dont une paupière est suturée depuis l'enfance demeurent amblyopes si cet œil est ouvert à l'âge adulte. Cependant, ces derniers peuvent retrouver une acuité visuelle équivalente à l'œil contrôle s'ils suivent un régime de restriction calorique pendant un mois, débutant deux semaines avant l'ouverture de la paupière. Les auteurs ont également démontré que cette plasticité est dépendante du stress généré par la restriction de nourriture, ce qui engendre une augmentation de corticostérone et une réduction de l'inhibition GABAergique. Le besoin de manger s'apparente donc à une « période critique » dans la vie de l'animal, permettant à d'autres circuits neuronaux d'étendre ou de déclencher de nouvelles fenêtres temporelles de plasticité.

3.1 Plasticité périphérique

Le système gustatif périphérique est particulièrement susceptible aux pressions environnementales (Hill, 2004). Les plus beaux exemples de plasticité sont liés soit à l'adaptation d'un environnement extérieur hostile ou à l'adaptation d'un changement homéostatique. Par exemple, l'exposition continuelle à la caféine chez la chenille induit une atténuation de la réponse seulement chez les récepteurs gustatifs (présents sur la surface du corps) sélectifs à l'amertume (Glendinning *et al*., 1999). D'un autre côté, consommer une diète pauvre en sodium durant dix jours pourra provoquer chez le rat la multitude d'effets ci-dessous (revue dans Hill, 2004):

- réduction de la taille des papilles gustatives
- réduction du nombre de cellules gustatives
- changement de la cinétique des cellules gustatives
- réduction de la réponse de la corde du tympan
- réduction de la réponse du noyau du faisceau solitaire

- augmentation de la taille et irrégularité des champs terminaux de la corde du tympan et du nerf glossopharyngien (mais pas du grand nerf pétreux) dans le noyau du faisceau solitaire, particulièrement dans sa section dorsale
- augmentation du nombre et de la longueur des dendrites des neurones situés dans le pôle rostral du noyau du faisceau solitaire
- changements hormonaux contrôlant l'équilibre du sodium, dont une production accrue d'aldostérone (régulateur des canaux sodiques) par les glandes surrénales et une possible augmentation de canaux sodiques.

À l'exception des changements plastiques observés dans le premier relais gustatif du système nerveux central, ces effets sont facilement réversibles à l'intérieur de 2 semaines, suivant le retour à une diète normale et riche en sodium. Cette plasticité s'explique notamment par le renouvellement des récepteurs gustatifs qui nécessite environ la même période (Hill, 2004).

Le degré et l'étendue de cette plasticité dépendent de plusieurs facteurs, dont l'âge de l'animal et la structure gustative impliquée. Tel que mentionné plus haut, c'est durant le développement embryonnaire qu'elle atteint son paroxysme. Par exemple, si la rate gestante se nourrit d'une diète pauvre en sodium avant l'apparition des papilles gustatives sur la portion antérieure de la langue de ses ratons (soit au 8^{e} jour embryonnaire) et que cette diète est maintenue jusqu'au sevrage (28^{e} jour postpartum), la réponse de la corde du tympan au sodium sera réduite de 60% chez ces ratons comparés aux contrôles (Hill, 2004). Similairement, le gavage intra-gastrique sans stimulation gustative orale autre que par l'eau chez les ratons nouveau-nés altère l'organisation des projections vers le tronc cérébral (Lasiter, 1995). D'autre part, les nerfs de la cavité orale présentent une susceptibilité différente à la plasticité. Il est intéressant de noter que parmi les trois nerfs gustatifs stimulés par la nourriture mise en bouche, c'est la cordé du tympan soit celui innervant la structure la plus mobile de la cavité orale (langue antérieure) qui est le plus affecté, suivi par le nerf glossopharyngien (langue postérieure). Le grand nerf superficiel pétreux (palais) ne démontre pour sa part aucun changement relié aux modifications de la diète de l'animal (Hill, 2004).

La plasticité induite par la diète peut aussi s'observer chez le rat adulte à condition que l'animal subisse une lésion au nerf gustatif. Par exemple, suivant la régénération de la cordée du tympan de 40 à 120 jours suivant une lésion unilatérale, les nerfs ipsi- et controlatéral

deviennent respectivement hyposensible (baisse de 30% de la réponse) et hypersensible seulement chez les animaux lésés alimentés par une diète pauvre en sodium, tandis que les animaux contrôles lésés ou alimentés par la même diète présentent des réponses normales (Hill & Phillips, 1994).

Alors que la régénération de la cordée du tympan est plutôt robuste chez le rat, elle ne l'est pas autant chez l'humain (Barry & Frank, 1992). Les patients nécessitant une opération à l'oreille moyenne subissent souvent une lésion accidentelle de ce nerf gustatif important, ce qui décroit leur sensibilité aux goûts (Just *et al*., 2006; Saito *et al*., 2012). Alors qu'environ 60% des patients pédiatriques bénéficient d'une régénération du nerf lésé, ce ratio passe à près de 30% chez le patient adulte. De ces derniers, seulement les deux-tiers des enfants et le tiers des adultes bénéficieront d'un rétablissement de leur sensibilité gustative préopératoire (Saito *et al*., 2012). Par ailleurs, l'endoscopie par contact lingual a permis d'observer des changements morphologiques aux papilles fongiformes ipsilatérales à la lésion chez des patients adultes. Celles-ci sont non seulement moins nombreuses mais évoluent du rond vers le filiforme comparativement au côté controlatéral à la lésion ou aux patients contrôles (Just *et al*., 2006).

Les changements morphologiques aux papilles gustatives peuvent aussi être induits par la consommation d'aliments ou de drogues. Par exemple, les papilles fongiformes des fumeurs sont davantage kératinisées comparées à celles des non-fumeurs. De plus, la sensibilité à l'amertume est altérée par le tabac de sorte que les fumeurs tendent à identifier les composés amers moins bien que les non-fumeurs (Konstantinidis *et al.*, 2010). Heureusement, les sensibilités olfactives et gustatives s'améliorent suivant le sevrage tabagique comme le démontrent souvent les témoignages d'ex-fumeurs qui se réjouissent de pouvoir mieux savourer leurs repas.

La consommation affecte fortement les sensibilités aux goûts. Le meilleur exemple concerne le goût umami, mieux connu chez les populations asiatiques qui utilisent régulièrement le glutamate monosodique (GMS, un composé umami) comme rehausseur de goût à l'instar du sel et du poivre. Kobayashi et collègues (2002, 2006) ont démontré des différences culturelles de sensibilité gustatives entre Américains/Européens et Asiatiques. Suivant une exposition de 10 jours à des craquelins aux crevettes contenant du GMS (vs

groupe contrôle exposé à des chocolats), les Américains/Européens exposés au GMS montraient des seuils d'identification plus bas à la fin des 10 jours. Cependant, ces seuils étaient plus hauts comparativement aux Asiatiques fortement exposés à l'umami à travers leur alimentation (Kobayashi & Kennedy, 2002). Plus intéressant encore, l'interruption de l'exposition à l'umami durant 10 jours additionnels s'est révélée suffisante pour rétablir les seuils d'identification aux niveaux initiaux, indiquant que la plasticité induite par la diète est réversible (Kobayashi *et al*., 2006). Bien qu'il soit possible que des mécanismes centraux aient joué un rôle, le renouvèlement des récepteurs gustatifs au niveau périphérique a certainement contribué à cette plasticité induite par la diète.

3.2 Plasticités centrale et intermodale

3.2.1 Aversion conditionnée au goût

L'exemple le plus éloquent de plasticité gustative au niveau du système nerveux central est sans doute celui de l'aversion conditionnée au goût. Ce paradigme d'apprentissage décrit le rejet d'une nourriture (stimulus conditionné; SC) préalablement considérée comestible suite à son association à un malaise comme la nausée ou une maladie (stimulus non-conditionné; SN). Contrairement aux autres modalités dans lesquelles le délais d'appariement du SC et SN est très critique et optimal seulement entre 500 ms et 2 s, l'aversion conditionnée à un goût s'encode même après un délais de 30 min à quelques heures (Bernstein, 1999). Ce délai correspond au temps de digestion des aliments et permet au système gustatif d'encoder les conséquences aversives rencontrées à tous les niveaux du tractus gastro-intestinal. De plus, l'apprentissage de l'aversion conditionnée a la particularité de s'acquérir de manière très robuste après un seul essai, du moins chez le rongeur. Ceci reflète sans doute la menace des aversions sur l'homéostasie et le maintien de la vie, en particulier chez les espèces incapables de vomir (non-émétiques). Enfin, elle est conservée chez les animaux, incluant les invertébrés, et s'acquiert même sous anesthésie générale chez le mammifère, démontrant l'implication de la mémoire implicite (inconsciente) plutôt qu'explicite (consciente).

Les mécanismes neuronaux de l'aversion conditionnée au goût ou à une nourriture ont été étudiés surtout chez le rat, une espèce comptant un relais gustatif supplémentaire (le PBN)

comparé à l'Homme. Bien que les lésions totales du NFS soient pratiquement impossibles en raison de ses fonctions vitales, les lésions partielles ne perturbent pas l'aversion conditionnée à un goût. Cependant, celles du PBN empêchent l'acquisition de l'aversion conditionnée à une nourriture sans affecter pour autant son expression. L'*aera postrema*, impliquée notamment dans la détection de toxines dans le sang, est essentielle à certaines aversions conditionnées puisqu'elle est spécifique à seulement quelques toxines. Finalement, les lésions à l'amygdale et l'insula atténuent l'aversion conditionnée à une nourriture (Bernstein, 1999). Tel que suggéré par Yamamoto (1993), il semblerait que le circuit liant le noyau ventrolatéral du PBN à la partie latérale de l'amygdale en passant par le thalamus médial soit responsable de l'aversion conditionnée au goût et implique la potentialisation et la dépression à long terme au niveau du PBN.

Chez l'humain, l'aversion conditionnée à un goût ou une nourriture est problématique chez les patients cancéreux. Ces derniers perdent l'appétit et refusent de manger à nouveau les repas servis avant leurs traitements de chimiothérapie, ce qui entraine une anorexie voire même une cachexie. Pour y remédier, certains pédiatres encouragent la consommation additionnelle de bonbons avant la chimiothérapie. Ces bonbons prennent alors le rôle de bouc émissaire et la nourriture consommée avant un traitement conserve ses propriétés non-aversives lors de présentations ultérieures (Bernstein, 1999).

3.2.2 Transmission sociale des préférences alimentaires

Alors que l'aversion conditionnée à une nourriture se développe chez un seul individu exposé aux goûts (ou saveurs), l'aversion et l'affection envers certains aliments peut aussi se transmettre entre individus, seulement par exposition aux indices extéroceptifs, tels que les odeurs présentées par voie orthonasale. La transmission sociale des préférences alimentaires (TSPA) s'effectue lorsque le choix alimentaire d'un animal observé est transmis à l'observateur lors d'un essai ultérieur. Cette tendance à copier ses semblables est absente chez le rongeur anosmique et implique le cortex gustatif primaire. Fortis-Santiago et collègues (2010) ont démontré que cette aire corticale n'attribue pas seulement la valeur incitative à une nourriture ni ne traite simplement l'information olfactive. Au contraire, le cortex gustatif primaire du rat encode les attributs gustatifs de stimuli olfactifs orthonasaux. Ainsi, si ce cortex est doublement inhibé durant l'encodage et l'expression de la TSPA, la TSPA est

maintenue, alors qu'elle est perdue s'il n'est inhibé qu'une seule fois (Fortis-Santiago *et al*., 2010; Yeshurun & Sobel, 2010).

Chez l'Homme, la TSPA implique en particulier la vision. Les choix alimentaires, tout comme la perte ou le gain de poids, sont transmissibles à travers les réseaux sociaux (Robinson *et al*., 2014). Manger en groupe augmente souvent la prise alimentaire, en particulier si les autres convives sont des amis ou membres de la famille (Herman *et al*., 2003). Barthomeuf *et al* (2010) ont démontré que le désir de consommer augmente chez l'individu qui regarde une autre personne souriante manger. De plus, si le visage du consommateur exprime le dégoût en mangeant, le désire de consommer décroit chez l'observateur. Cependant, ces effets disparaissent si le consommateur observé est obèse de sorte que le désir de manger chez l'observateur demeure faible, peu importe l'expression faciale du consommateur en surpoids.

3.2.3 Manipulations des prévisions

Les expressions corporelles de nos semblables envers la nourriture modulent nos préconceptions à l'égard des aliments. Celles-ci sont transmises de manière plus efficace via les langages parlé et écrit. L'Homme est particulièrement sensible à ce genre de manipulations comme le démontre explicitement l'effet placébo. Ce dernier décrit l'action thérapeutique d'une substance sans principe actif seulement par la description préalable de ses vertus. Récemment, Ellingsen et collègues (2013) ont démontré que l'effet placébo était efficace non seulement dans la réduction de la douleur (analgésie) mais aussi dans l'augmentation du plaisir (hyperhédonie). Ces deux mécanismes recrutent notamment les cortex orbitofrontal médial et cingulaire antérieur prégénual, tous deux impliqués dans la gustation (Veldhuizen *et al*., 2011a).

La description des goûts et des saveurs, fournies par nos semblables ou l'étiquetage, l'emballage et les menus de restaurants, influence directement les réponses du thalamus et des cortex primaire et secondaire gustatifs. Par exemple, faire croire à tort à un sujet qu'il recevra un goût amer moyennement aversif réduit le signal dans l'insula comparé au même stimulus correctement identifié comme ayant un goût très aversif (Nitschke *et al*., 2006). À l'opposé, faire croire à quelqu'un qu'il recevra un goût très sucré alors qu'il est en réalité moins sucré augmente la réponse dans l'insula comparé au même stimulus correctement étiqueté

(Veldhuizen *et al*., 2011b; Woods *et al*., 2011). La réponse BOLD (signal dépendant du niveau d'oxygène sanguin) du COF médial peut aussi être manipulée de façon similaire en augmentant par exemple le prix d'un vin (Plassman *et al*., 2008). Ces données d'imagerie se reflètent du côté comportemental par des évaluations subjectives d'intensité (Nitschke *et al*., 2006; Veldhuizen *et al*., 2011b; Woods *et al*., 2011) ou de plaisir (Plassman *et al*., 2008) qui concordent avec les descriptions préalables.

Chez le rat qui se crée des attentes par conditionnement (ex : appariement de goûts avec signaux auditifs), ce type de modifications de réponses dans le cortex gustatif primaire sont causées par l'influence descendante de l'amygdale qui traite des signaux anticipatoires (Samuelsen *et al*., 2012). Samuelsen et collègues ont par ailleurs démontré que les neurones du cortex gustatif primaire pouvaient se subdiviser en deux populations, dépendamment de leur sensibilité aux indices anticipatoires (Samuelsen *et al*., 2012; Zelano & Gottfried, 2012). Ainsi, suivant l'inactivation du thalamus gustatif, la réponse du cortex gustatif primaire est largement diminuée pour des goûts imprédictibles mais demeure pratiquement inchangée pour les stimuli prédictibles. Ceci suggère qu'il y ait deux voies gustatives, la première thalamocorticale et la deuxième impliquant les structures limbiques et évitant le thalamus (Allen *et al*., 1991; Samuelsen *et al*., 2013; Stone *et al*., 2011).

Chez l'Homme, l'amygdale et le thalamus répondent davantage aux odeurs prédisant l'arrivée immédiate de leurs saveurs associées comparées aux mêmes odeurs suivies d'une présentation de solution insapide ou aux mêmes saveurs non précédées par leurs odeurs orthonasales (Small *et al*., 2008). Les structures impliquées dans les phases d'anticipation et de consommation sont latéralisées et se chevauchent dans le cerveau de sorte que l'insula/opercule gauche répond davantage à un breuvage (consommation) alors que l'insula/opercule droit et le COF répondent à ce même breuvage précédé ou non de son odeur orthonasale (anticipation et consommation; Small *et al*., 2008).

3.2.4 Interactions vision-goût

Il est très facile de manipuler les attentes, les perceptions gustatives tout comme l'expérience alimentaire par l'aspect visuel, consciemment ou inconsciemment. Les jeunes parents et les chefs cuisiniers le savent d'ailleurs très bien. Pour rendre un brocoli intéressant à son enfant récalcitrant, une mère rusée peut le tailler en forme d'animal et la même nourriture

prend alors un tout autre attrait. En restauration, le côté artistique de la présentation qui mélange équilibre et complexité est essentiel pour s'assurer d'une clientèle satisfaite (Michel *et al*., 2014; Zellner *et al*., 2010, 2011). Cet appel des sens par la nourriture tout comme sa mise en contexte influencent directement la prise alimentaire mais aussi les perceptions gustatives, mesurées autant par les points de vue subjectif qu'objectif. Ainsi, changer l'éclairage ambiant de sorte à transformer les couleurs d'un steak brun, de pois verts et de pommes de terre frites jaunes respectivement vers le bleu, le rouge et le vert aura pour effet de provoquer la nausée chez les consommateurs, au point d'en rendre malades certains (Wheatley, 1973). Au contraire, favoriser un éclairage (et une musique) doux et agréable(s) augmente la satisfaction des repas (Wansink & Van Ittersum, 2012). Du point de vue objectif, le simple fait d'ajouter quelques gouttes de colorant alimentaire insipide à de l'eau sucrée est suffisant pour modifier le seuil de perception gustative ainsi que les jugements d'intensité, et ceci même si les participants considèrent les couleurs comme des informations hors sujet (revues dans Spence *et al*., 2010; Verhagen & Engelen, 2006).

Les formes et textures influencent également les perceptions gustatives. Lorsque les consommateurs sont exposés à des textures visuelles (ex : texture de fraise) et des saveurs (ex : eau sucrée à la fraise) congruentes simultanément, ces derniers perçoivent la nourriture plus sucrée. Cet effet est augmenté lorsque les textures deviennent des figures reconnaissables (ex : fraise; Van Beilen *et al*., 2011). Par ailleurs, regarder des formes géométriques courbes telles que des cercles ou ellipses facilite la détection du sucrose comparativement aux formes angulaires (ex : carré, pentagone; Liang *et al*., 2013).

L'effet des couleurs et des formes sur la gustation n'est pas limité à la nourriture mais s'étend aussi à la vaisselle et la coutellerie utilisées lors des repas. Par exemple, un maïs soufflé salé sera perçu plus sucré s'il est servi dans un bol coloré comparativement à un bol blanc (Harrar *et al*., 2011). Similairement, manger un dessert à l'aide d'ustensile ou de vaisselle noir(e) plutôt que blanc(he) décroît la perception sucrée (Harrar & Spence, 2013; Piqueras-Fiszman *et al*., 2012; voir aussi Stewart & Gross, 2013). Boire un chocolat chaud servi dans une tasse orange plutôt que blanche, noire, crème ou rouge augmente l'appréciation et l'intensité savoureuse (Piqueras-Fiszman, 2012). La forme et la qualité des assiettes comme de la coutellerie influence également les perceptions gustatives (Harrar & Spence, 2013; Piqueras-Fiszman *et al*., 2012). Par exemple, consommer un yogourt avec un couteau

augmente sa perception salée comparativement au même aliment mangé à l'aide d'une cuiller, d'un cure-dent ou d'une fourchette (Harrar & Spence, 2013).

Finalement, la vision est aussi importante pour terminer les repas. Bien que la décision d'arrêter de manger devrait surtout être gouvernée par les sensations de faim et de satiété du consommateur, l'étiquette exige trop souvent de terminer le contenu de l'assiette, parfois même sous la menace de ne pas mériter de dessert. Cette attitude non intuitive (Tylka, 2006) encourage l'absorption de nourriture superflue, spécialement dans les pays où la nourriture est omniprésente et les portions gigantesques. Ainsi, augmenter la disponibilité de nourriture dans l'assiette sans que le consommateur s'en aperçoive (ex : bol de soupe qui s'auto-remplit) est orexigène (Wansink *et al*., 2005) alors que pouvoir surveiller par le regard au cours d'un repas la quantité d'aliments ingurgités (ex : présence vs retrait des os de poulet désossés) a l'effet contraire (Wansink & Payne, 2007).

3.2.5 Interactions odorat-goût

Les perceptions gustatives peuvent aussi être augmentées par l'addition d'odeurs congruentes à un mélange savoureux. Dalton *et al*., 2000 ont démontré qu'il est possible de détecter la présence de saccharine dans un mélange de cet édulcorant sucré et de benzaldéhyde (parfum de cerise) lorsque ces derniers sont tous les deux présents dans l'eau à des concentrations en deçà de leur seuil de détection respectif. Cependant, cet effet additif disparaît pour des mélanges incongrus, par exemple dans des mixtures de GMS et de benzaldéhyde. Similairement, sentir via la voie orthonasale ou imaginer des odeurs congruentes aux goûts facilite la détection de goûts et en augmente leur jugement d'intensité (Djordjevic *et al*., 2004ab). Plus une odeur est qualifiée sucrée, plus elle sera efficace pour augmenter la perception sucrée d'un mélange de sucre ou diminuer la perception acide d'un mélange d'acide (Verhagen & Engelen, 2006).

La satiété sensorielle spécifique à un aliment est aussi possible seulement suite à une exposition olfactive orthonasale, sans même mettre en bouche la nourriture ciblée. Par exemple, plus quelqu'un respire longtemps le parfum de banane par ses narines, plus le plaisir évoqué par ce fruit décroitra (Rolls, 2011), sans changer pour autant les évaluations hédoniques des autres aliments.

Prises en considération, ces études démontrent que goûter non seulement dépend des autres sens mais interagit fortement avec eux. Qu'arrive-t-il alors au sens du goût suivant la perte d'un sens comme la vision? Les sections suivantes répondent à cette question.

4. PROBLÉMATIQUES ET HYPOTHÈSES

4.1 La consommation et le goût chez l'aveugle

L'absence de vision a certainement un impact important sur la consommation alimentaire comme la gustation. Peu d'études y ont par contre été dédiées. La plus important est sans doute celle de Bilyk *et al*. (2009) qui, par le biais d'entrevues semi-structurées, ont relevé plusieurs obstacles reliés au handicap visuel chez des malvoyants Canadiens lorsque vient le temps de faire leur épicerie, choisir et préparer leur nourriture ou même manger dans des restaurants. Par exemples, non seulement les emballages limitent la quantité d'indices sensoriels (parfums, textures, etc.) facilitant l'identification des aliments mais cuisiner des repas est un processus lent et ardu qui comporte plusieurs dangers (ex : couteaux tranchants, sources de chaleur). Les restaurants n'offrent pour leur part que très rarement des menus en Braille. Par conséquent, les personnes ayant une basse vision se trouvent trop souvent dépendantes de leur entourage pour faire l'épicerie, choisir et préparer leur nourriture, ce qui peut engendrer nombreuses frustrations en plus de restreindre la variété de leur diète.

À table, la microstructure du comportement alimentaire avec et sans la vision a été étudiée par Linné et collègues (2002) auprès de neuf sujets aveugles précoces et neuf autres voyants aux yeux ouverts ou bandés. Grâce à une balance connectée à un ordinateur, les chercheurs ont mesuré la prise alimentaire (en g), sa durée (min) de même que sa vitesse (g/min) et sa décélération (g/min^2) au cours d'un repas. Bander les yeux de sujets voyants influence grandement leur prise alimentaire, de sorte que ces derniers mangent moins de nourriture alors que leur repas dure moins longtemps. De plus, ils décélèrent leur prise alimentaire plus lentement que s'ils avaient les yeux ouverts. Pour leur part, les aveugles précoces mangent beaucoup plus lentement et tendent à prolonger la durée de leur repas comparativement aux sujets voyants avec les yeux ouverts. D'autres chercheurs ont cependant trouvé des résultats opposés lorsque les sujets étaient testés dans des environnements naturels.

Bien que certains paramètres n'aient pas été contrôlés, en particulier la présence d'autres personnes à table qui peut influencer à la hausse la quantité de nourriture ingurgitée (Herman *et al*., 2003), Scheibehenne *et al*., (2010) ont trouvé que les participants mangeaient davantage de nourriture et ce, pendant plus longtemps, si le restaurant était plongé dans le noir comparé à si ce dernier était éclairé. Dans le même esprit, bander les yeux d'un voyant durant la consommation réduit sa satiété sensorielle-spécifique comparée à la condition avec les yeux ouverts (Havermans & Mallach, 2014). En d'autres termes, la décroissance de l'évaluation hédonique de l'aspect visuel d'un aliment suite à sa consommation est plus petite quand ce dernier est mangé avec les yeux fermés (Havermans & Mallach, 2014), ce qui risque en retour d'augmenter la quantité consommée de cette nourriture si elle est mangée *ad libitum*.

Manger dans le noir ou avec les yeux bandés a un autre impact important sur la gustation, ou plutôt sur son milieu de référence, à savoir la salive. Les flux salivaires stimulé et non-stimulé par la nourriture (ex : gomme à mâcher) diminuent immédiatement d'au moins 70% suivant une exposition à la noirceur et cette baisse est maintenue même après une adaptation scotopique de 20 minutes (Dong & Dawes, 1995; Shannon *et al*., 1972; Shannon & Suddick, 1973). Cependant, les aveugles sans (ou avec) perception lumineuse présentent des flux salivaires comparables aux sujets contrôles exposés à la lumière, pointant vers une adaptation à long terme bénéfique chez les non-voyants (Dong & Dawes, 1995).

Du côté de la capacité à détecter ou identifier des solutions gouteuses (sucrée, salée, acide et amère), Schutte et Zubek (1967) ont démontré que porter un bandeau sur les yeux pendant une semaine augmente la sensibilité au sucré et au salé chez les voyants, sans changer pour autant leurs sensibilités à l'acide et à l'amertume. Cet effet persiste même après une journée d'exposition à la lumière. Malheureusement, ces chercheurs n'ont pas contrôlé pour le niveau de salive qui est aussi affecté par la noirceur. Si les sujets aux yeux bandés produisent moins de solvant naturel que les contrôles aux yeux ouverts, il leur sera plus facile de détecter les solutés une fois mis en bouche, puisque la concentration orale du même stimulus sera alors plus élevée. Chez l'aveugle, Smith *et al.* (1993) n'ont pas trouvé de différences entre une cinquantaine de non-voyants et une vingtaine de contrôles dans leurs habiletés à reconnaître les goûts de base ni dans leur évaluation sensorielle (intensité) et hédonique. Bien que cette étude contienne de larges effectifs, elle a aussi plusieurs faiblesses. La première est le choix des tâches qui consistent à reconnaître ou évaluer des goûts à des concentrations bien au-

dessus des seuils de perception gustatifs. Ces tâches ont été normalisées et validées pour la clinique dans le but de diagnostiquer des patients atteints de dysfonctions chimiosensorielles, dont des troubles gustatifs (Smith, 1988). Puisque les sujets aveugles sont normogueusiques (sans trouble gustatif) autant que les voyants, la méthode risque de ne pas être assez sensible pour détecter des différences perceptuelles entre ces deux groupes. La deuxième critique est l'hétérogénéité du groupe d'aveugles qui rassemble autant de sujets congénitaux que tardifs, aux étiologies et aux durées de cécité variées. Hors, d'après le principe Kennard (Dennis, 2010), le degré de plasticité varie en fonction de l'âge d'acquisition de la cécité et de sa durée, celui-ci étant maximal chez les aveugles congénitaux les plus âgés. Il est donc possible qu'un sous-groupe d'aveugles performe différemment des autres, ce qui risque d'être masqué en groupant tous les aveugles ensemble.

4.2 Pertinence du projet

Ensemble, ces études indiquent que nous savons très peu de chose sur le goût chez l'aveugle. Ceci est surprenant puisque les aveugles vivent trop souvent dans des conditions de vie précaires, souffrent d'isolement, de troubles du sommeil, parfois aussi de dépression et d'anxiété (en particulier chez les aveugles tardifs) ainsi que d'une pauvre qualité de vie (Bolat *et al*., 2011; Boulton *et al*., 2006; Huurre & Aro, 1998; Jones *et al*., 2009; Nyman *et al*., 2012; Tabandeh *et al*., 1998). Or, la consommation est une activité sociale et le développement du goût (ainsi que de l'olfaction rétronasale) comme l'apprentissage de la gastronomie sont associés à une bonne santé et une haute qualité de vie (Baharvand *et al*., 2013; Brillat-Savarin, 1826; Hummel & Nordin, 2005;). De plus, la stimulation du système gustatif par de la nourriture plaisante a le pouvoir de réinitialiser l'horloge biologique si cette dernière est consommée à des périodes fixes de la journée (Tanaka *et al*., 1999). À l'inverse et tel que décrit plus tôt, la paupérisation gustative allonge les périodes critiques de plasticité du système visuel et favorise la guérison de l'amblyopie, même chez l'animal adulte (Spolidoro *et al*., 2011). Finalement, la connaissance des aliments, de leurs vertus et les choix nutritionnels optimaux ont le pouvoir de prévenir et guérir certaines maladies oculaires (Akhtar *et al*., 2013; Pelletier & Capogna, 2011). L'étude du goût et de l'alimentation promet donc une panoplie de

solutions pour contrer les problèmes rencontrés chez les personnes à risque ou ayant des troubles visuels.

4.3 Hypothèses et justification des méthodes

Puisque la vision influence grandement la consommation alimentaire et les perceptions gustatives, il est raisonnable de supposer que la perte de vision aura des conséquences importantes sur cette modalité et les habitudes alimentaires. Le but principal de la présente thèse est donc d'investiguer l'effet de la privation visuelle depuis la naissance sur le sens du goût. Il se décompose en sous-objectifs suivants, adressés dans les cinq manuscrits du corps de cet ouvrage.

Article 1

La diète restreinte et l'expérience limitée des aveugles avec la nourriture (Bilyk *et al*., 2009) diminuera-t-elle leur sensibilité gustative comparativement aux sujets contrôles voyants? Pour répondre à cette question, les seuils de perception gustatifs (détection et identification) des cinq goûts de base sont évalués chez des aveugles congénitaux et des contrôles voyants aux yeux bandés à l'aide de la technique du « *sip and spit* ». Cette dernière consiste à boire et recracher en alternance des échantillons de 5 mL d'eau et de solution gouteuse à différentes concentrations. Elle a l'avantage de stimuler la bouche entière telle que c'est le cas lors de la consommation d'un breuvage. De plus, la sensibilité de la méthode est ajustée pour tester des différences entre populations normogueusiques (Hong *et al*., 2005). Finalement, le niveau de salive sera contrôlé dans les deux groupes en utilisant un bandeau photopique qui laisse passer la lumière et brouille la vision.

L'absence de vision depuis la naissance modifiera-t-elle les habitudes alimentaires de sorte à augmenter les degrés de consommation intuitive et de néophobie tout en diminuant la recherche de variété dans la diète? Ces habitudes alimentaires seront évaluées et comparées entre les groupes à l'aide de questionnaires (Tylka, 2006; Pliner & Hobden, 1992; Van Trijp & Steenkamp, 1992). Enfin, puisque le système gustatif est considéré par certain chercheur (Craig, 2002) comme un système intéroceptif plus large, la conscience du corps sera aussi

évaluée et comparée entre les groupes à l'aide d'une échelle développée par Shields *et al*. (1989).

Article 2

Comme le goût participe avec l'olfaction rétronasale à la perception unifiée de saveurs, le deuxième article vise à investiguer les habiletés à savourer, principalement avec le nez, chez les aveugles et voyants. Notre hypothèse suggère que les aveugles identifient moins bien que les voyants les odeurs présentées via la voie rétronasale tout en performant mieux – comme cela a déjà été démontré (Cuevas *et al*., 2009; Murphy & Cain, 1986; Rombaux *et al*., 2010) – dans l'identification des odeurs orthonasales. Pour tester cette prémisse, les participants aveugles et voyants aux yeux bandés devront identifier différentes nourritures sèches réduites en poudre présentées sous les narines (orthonasale) ou sur la langue (rétronasale). À cet effet, le protocole de Heilmann et Hummel (2004) à été modifié de façon à inclure une plus grande quantité d'odeurs qui stimulent les deux (plutôt qu'une) voies olfactives. De plus, la méthode a été adaptée aux populations normosmiques en augmentant la difficulté de la tâche (identification sans choix de réponse) et en mesurant leurs temps de réponses.

Article 3

Comme les aveugles détectent et identifient moins bien les goûts que les voyants, ceci suggère que les corrélats neuronaux diffèrent entre les groupes. Notre hypothèse d'imagerie suggère que les aveugles congénitaux activent plus faiblement leur(s) cortex gustatif(s) en goutant. Pour répondre à cette question, la technique d'imagerie par résonance magnétique fonctionnelle (IRMf) sera utilisée alors que les participants évaluent l'intensité ou le plaisir évoqué par des solutions sucrées (typiquement plaisantes), amères (déplaisantes) ou neutre. Cette technique a l'avantage d'être non-invasive et mesure l'activité du cerveau entier, incluant les structures profondes comme l'insula, tout en offrant des résolutions temporelle et spatiale optimales.

Article 4

L'article 4 vise à étudier la plasticité du système gustatif suivant une autre perte sensorielle, soit la déficience olfactive depuis la naissance, qui montre également des

diminutions de performance en gustation (Levy *et al*., 2013). Notre hypothèse suggère que les sujets atteints d'une déficience olfactive congénitale activent plus faiblement que les sujets contrôles normosmiques leur cortex gustatif durant l'identification de solutions sucrée, salée, amère ou neutre. La même technique de l'article 3 sera utilisée.

Article 5

Enfin, l'article 5 résume la littérature portant sur les effets de la plasticité intermodale impliquant les sens chimiques (l'odorat, la gustation et le sens trigéminal) chez l'aveugle congénital et les compare à ceux observés chez le voyant normosmique de même que chez le voyant anosmique congénital.

5. CONTRIBUTIONS DES AUTEURS

Cette thèse a été réalisée en collaboration avec le Brain Research And Integrative Neuroscience (BRAIN) Laboratory du Département de Neurosciences et Pharmacologie de l'Université de Copenhague (KU). De plus, l'article 4 est issu d'un projet multidisciplinaire de neuroimagerie et de génétique incluant le Danish Research Centre for Magnetic Resonance de l'Hôpital de Hvidovre ainsi que le Wilhelm Johannsen Centre for Functional Genome Research du Département de Médecine Cellulaire et Moléculaire de KU. La contribution des auteurs est expliquée en détails ci-après :

Article 1 : Reduced taste sensitivity in congenital blindness

RK et MP ont eu l'idée originale. LG a mis au point le protocole, collecté (avec l'assistance de Mina Smiljkovic), analysé et interprété les données en plus de rédiger et corriger le manuscrit. RK et MP ont critiqué, corrigé et révisé le manuscrit.

Article 2 : Superior orthonasal but not retronasal olfactory skills in congenital blindness

RK a eu l'idée originale et LG a raffiné le protocole. LG et ARAI ont collecté les données. LG a analysé et interprété les données en plus de rédiger et corriger le manuscrit suivant les critiques et commentaires de RK et MP.

Article 3 : Neural correlates of taste perception in congenital blindness

LG, RK et MP ont mis au point le protocole. LG a collecté (avec l'assistance de Sébrina Aubin et de la technicienne), analysé et interprété les données en plus de rédiger et corriger le manuscrit suivant les critiques et commentaires de RK et MP.

Article 4 : Neural correlates of taste perception in congenital olfactory impairment

HS, RK et MP ont eu l'idée originale. KM et LG ont mis sur pied le protocole. KHG a recruté les participants. LG, MV et KHG ont récolté les données (avec l'assistance de la technicienne). LG, KM et MV ont analysé les données (prétraitement: KM; analyses fonctionnelles: LG; analyses volumétriques: MV). LG et MV ont interprété les données. LG a rédigé et corrigé le manuscrit et MV a écrit le matériel supplémentaire. MP et RK ont critiqué et corrigé le manuscrit alors que NT, HS, KM et HGK l'ont approuvé.

Article 5 : Making sense of the chemical senses

LG a rédigé le manuscrit, MP, RK et LG l'ont corrigé.

Article 1

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Reduced taste sensitivity in congenital blindness

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Abstract

Sight is undoubtedly not only important for food identification and selection but also for the modulation of gustatory sensitivity. We can, therefore, assume that taste sensitivity and eating habits are affected by visual deprivation from birth. We measured taste detection and identification thresholds of the 5 basic tastants in 13 congenitally blind and 13 sighted control subjects. Participants also answered several eating habits questionnaires, including the Food Neophobia Scale, the Food Variety Seeking Tendency Scale, the Intuitive Eating Scale, and the Body Awareness Questionnaire. Our behavioral results showed that compared with the normal sighted, blind subjects have increased thresholds for taste detection and taste identification. This finding is at odds with the superior performance of congenitally blind subjects in several tactile, auditory and olfactory tasks. Our psychometric data further indicate that blind subjects more strongly rely on internal hunger and satiety cues, instead of external contextual or emotional cues, to decide when and what to eat. We suggest that the lower taste sensitivity observed in congenitally blind individuals is due to various blindness-related obstacles when shopping for food, cooking and eating out, all of which contribute to underexpose the gustatory system to a larger variety of taste stimuli.

Key words: food neophobia, intuitive eating, multisensory integration, plasticity, taste thresholds, vision.

Introduction

The taste system is divided into a parallel "sensory" and "hedonic" pathway. Although the former codes taste quality (e.g. sweet), flavor (combination of smell, taste and trigeminal qualities) and texture, the latter is involved in the rewarding or aversive aspects of eating (Sewards, 2004). Both of these taste pathways are strongly affected by vision (Linne *et al*., 2002; Barkeling *et al.*, 2003; Ferriday and Brunstrom, 2008; Yeomans *et al.*, 2008; Barthomeuf *et al*., 2010; Piech *et al.*, 2010; Van Beilen *et al*., 2011; Barros-Loscertales *et al*., 2012; Bakalar, 2012; Delwiche, 2012; Ohla *et al.,* 2012; Zampini and Spence, 2012). As vision plays an important role in multisensory integration, it creates specific expectations about the flavor, viscosity, texture and sounds associated with the ingestion of foods. When the visual cues are congruent with those provided by other sensory modalities, they contribute to the acceptance and ingestion of food. Visual cues also influence taste and flavor intensity ratings (Spence *et al*., 2010). For example, adding color to a sweet water solution increases the taste threshold even if subjects are firmly instructed to ignore it (Verhagen and Engelen, 2006). Changing food colors while eating with special light (e.g. brown steak turning blue) can have aversive consequences like creating nausea (Wheatley, 1973). Sight also prepares the body for digestion. During the cephalic phase response, the sight of food triggers salivation and increases gastric acid secretion as well as serum gastrin concentrations (Feldman and Richardson, 1986; Powley, 2000). All this suggests that blind subjects may respond differently to tastants compared with normally sighted subjects. In addition, blind individuals experience a number of important obstacles when they shop for food, prepare meals or eat out (Bilyk *et al*., 2009), possibly leading to a less varied diet and a reduced exposure to different tastants and flavors compared with sighted subjects.

The few studies that have been done on the effect of vision loss on taste sensitivity have reported quite contradictory results. Although some studies (Mahner, 1909; Terner *et al.* 1987) have reported superior taste abilities in blind subjects, other studies (Smith *et al.*, 1993) found no differences between blind and sighted control subjects. This inconsistency may be explained by methodological issues such as the choice of tastants (with possible olfactory and trigeminal components), the limited number of study participants and the inclusion of blind subjects with taste disorders. The aim of this study was, therefore, to measure taste detection and identification thresholds, and various aspects of eating habits and body awareness in a

relatively large and homogeneous sample of congenitally blind and sighted control subjects. We hypothesized that compared to sighted controls, blind subjects would have higher taste thresholds, score higher on food neophobia attitude and intuitive eating, but lower on food variety-seeking tendency.

Methods

Participants

Psychophysics

A total of 15 congenitally blind and 13 normal sighted control subjects participated in the study. Table 1 summarizes the demographic data and causes of blindness. Two normally functioning blind participants with normal sense of taste but suffering from a neurological disorder (epilepsy or possible unilateral trigeminal nerve lesion) did not participate in the psychophysical experiments and were kept only for the eating habits analysis. None of the other participants suffered from any condition that could affect taste perception such as a history of gastric problems, dry mouth, chronic sinusitis, chronic pulmonary disease, abnormal olfactory sense, diabetes, or neurological disorders. We used the generalized anxiety disorder scale (GAD-7) and the Patient Health Questionnaire (PHQ-9) to screen for anxiety and depression, respectively. These two conditions are known to affect taste sensitivity and eating patterns (Heath *et al.*, 2006; Aschenbrenner *et al.*, 2008). Two female blind participants scored higher than 15 on either the GAD-7 or the PHQ-9 and were removed from the analyses. We, therefore, included data of 11 blind (3 females; mean age: 36 ± 4 years; mean body mass index (BMI): 23.3 ± 1.1 kg/m^2) and 13 sighted control (6 females; mean age: 33 ± 4 years; mean BMI: 24.0 ± 0.7 kg/m^2) subjects in the analysis. The local ethics committee approved the study, and all subjects gave informed and written consent prior to testing.

Preparation of the tastants

We prepared 5 series of tastants with distilled and deionized water: sucrose (sweet, 1.7 x 10^{-4} to 7.2 x 10^{-1} M), sodium chloride (salty, 1.3 x 10^{-5} to 1.0 M), citric acid (acid, 4.3 x 10^{-7} to 3.2 x 10^{-2} M), quinine-hydrochloride (bitter, 7.6 x 10^{-8} to 3.2 x 10^{-4} M) and monosodium glutamate (MSG) (umami, 1.1 x 10^{-5} to 8.3 x 10^{-1} M). We first tested the protocol of Hong and colleagues (2005) in a pilot experiment and adapted the range of concentrations (40 grades

instead of 30) of some tastants to the taste sensitivity of individuals from West European countries. For the final series of tastants, successive dilutions that comprised a total of 30 (sweet, bitter) or 40 (salty, acid, umami) grades differed by 25% of the molar concentration (Hong *et al.*, 2005). Tastants were freshly prepared at room temperature before use.

Table 1. Demographic data of blind participants

Sex	Age	Education (years)	Etiology of blindness	Onset of blindness	Residual vision
F*+	58	13	Retinopathy of prematurity	Birth	None
F*+	63	9	Retinopathy of prematurity	Birth	None
F	43	14	Retinopathy of prematurity	Birth	Light
F	24	16	Retinopathy of prematurity	Birth	None
M	51	14	Retinopathy of prematurity	Birth	None
M	37	12	Unknown	Birth	None
M	26	13	Retinopathy of prematurity	Birth	None
M	21	12	Leber amaurosis	Birth	None
M	43	12	Meningitis	1 year	Light, shapes
M*	36	14	Retinopathy of prematurity	Birth	None
M*	44	24	Bilateral retinoblastoma	Birth	None
M	40	16	Retinopathy of prematurity	Birth	Light
M	59	16	Retinopathy of prematurity	Birth	None
F	29	13	Retinopathy of prematurity	Birth	None
M	20	12	Unknown	Birth	None

F, female; M, male.
Removed from the psychophysical (*) and eating habits (+) analyses.

Testing procedure

The experiment was conducted 1-2h after lunch. Participants were instructed to refrain from eating, drinking (except for water), or chewing gum 1h before the start of the experiment. Two separate sessions of approximately 3h each were required to complete the psychophysical assessments. In both sessions, we first conducted a familiarization period to ensure that participants could recognize all 5 basic tastes. During this period, subjects tasted the highest concentration of each tastant and were told its taste quality. After rinsing abundantly their mouth with distilled and de-ionized water, taste thresholds were measured in the following order: sweet, salty, acid, bitter and umami. Abundant rinsing was mandatory between taste thresholds measurement to avoid taste lingering. Finally, we performed a phenylthiocarbamide

(PTC) bitterness sensitivity assessment using a taste strip (Fischer Scientific). For 6 subjects (4 blind), we needed a third session to complete the psychophysical assessment.

Assessment of detection and identification thresholds

We used the 2-alternative forced choice "sip and spit" method (Hong *et al.*, 2005) to assess detection and identification taste thresholds. We randomly presented tastants and distilled water to the subject as 5-ml samples in a 25-ml plastic cup. Prior to each tasting cup, the participant first rinsed his/her mouth with distilled water. After sampling the 2 cups, he/she had to indicate which of the cups contained the tastant. The staircase procedure started with the previous participant's detection threshold and continued until the emergence of 3 reversals. The reversals were obtained by the participant's answers: following an incorrect answer, a higher concentration was offered, whereas 2 consecutive correct answers were followed by a lower concentration. The values of the last 2 reversals were then averaged to calculate the threshold. For the identification threshold measurement, the staircase procedure started with the participant's own detection threshold. A similar procedure was used as for the detection threshold except that in addition to designate which cup contained the tastant, the participant also had to correctly identify its taste quality. Sighted subjects were blindfolded in photopic conditions to avoid decrease of salivary flow (Bellavia and Gallara, 2000).

Eating habits questionnaires

Participants filled in a Danish version (translation, Supplementary material) of the following eating habits questionnaires:

- Food Neophobia Scale (FNS; Pliner and Hobden, 1992). This scale evaluates fear for unfamiliar food (e.g. "I am afraid to eat things I have never had before").
- Variety Seeking Tendency Scale (VARSEEK; Van Trijp and Steenkamp, 1992). The VARSEEK measures the variety of food intake (e.g. "When I eat out, I like to try the most unusual items, even if I am not sure I would like them").
- Intuitive Eating Scale (IES; Tylka, 2006). This scale assesses the reliance on physiological hunger and satiety cues rather than emotional or contextual cues (e.g. "I trust my body to tell me when/what/how much to eat").

- Body Awareness Questionnaire (BAQ; Shields *et al.*, 1989). The BAQ measures the attentiveness to normal and non-emotive body processes (e.g. "I am always aware of changes in my energy level when I eat certain foods").

Statistics

An overview of the various statistical analyses performed to assess group differences (sighted vs. blind; independent variable) is presented in Supplementary Table 1. We took sex, age, BMI and PTC-sensitivity into account as covariates because taste sensitivity varies as a function of gender (Boesveldt *et al.*, 2011), PTC sensitivity (Hong *et al.*, 2005), and declines with age (Boesveldt *et al.*, 2011) and BMI (Simchen *et al.*, 2006). For the analysis of the questionnaires, we considered age (Shields *et al*., 1989; Koivisto and Sjoden, 1996; Nicklaus *et al*., 2005), sex (Shields *et al*., 1989), BMI (Tylka, 2006), and the GAD-7 (Pliner and Hobden, 1992; Costanzo *et al*., 2001), PHQ-9 (Costanzo *et al*., 2001), VARSEEK (Pliner and Hobden, 1992) and FNS (Van Trijp and Steenkamp, 1992) scores as possible covariates (part B, Supplementary Table 1).

Results

Gustatory perception

Figure 1 illustrates taste detection and identification thresholds in the blind and sighted control subjects. As the dependent variable was not normally distributed, we performed the analysis on the logarithmic value of each individual taste threshold. We used a *t*-test instead of analysis of covariance (ANCOVA) to analyze the data where the postulate of homogeneity of regression was violated (Wilson and Carry, 1969). Table 2 shows group differences in the detection of sweet, salty and bitter in favor of the sighted controls but not for acid and umami. For the identification thresholds, only bitter reached significance, once again favoring the sighted control group. The final 3-way analysis of variance (ANOVA) revealed a significant effect of group favoring the sighted controls. Our data further show significant effects of task (taste identification > taste detection thresholds) and taste, indicating that the magnitude of the taste thresholds is tastant-dependent, but no significant interaction.

Table 2. Summary of the statistical results

	Statistical test	Used covariate(s)	Statistical values*
A) Taste sensitivity			
General[a]	Three-way ANOVA	-	Group effect: $F_{22,1}$ = 7.36; p = 0.013 Task effect: $F_{22,1}$ = 231.7; p < 0.0005 Taste effect: $F_{88,4}$ = 338.7; p < 0.0005
Detection[b]			
Sweet	Independent Student's *t*-test	-	$t(22)$ = -2.707; p = 0.013
Salty	Independent Student's *t*-test	-	$t(22)$ = -2.121; p = 0.038
Acid	Independent Student's *t*-test	-	$t(22)$ = -1.401; p = 0.175
Bitter	Independent Student's *t*-test	-	$t(22)$ = -3.683; p = 0.001
Umami	One-way ANCOVA	BMI	$F_{21,1}$ = 1.143; p = 0.297
Identification[b]		-	
Sweet	One-way ANOVA	-	$F_{22,1}$ = 0.340; p = 0.565
Salty	Independent Student's *t*-test	-	$t(22)$ = -1.192; p = 0.246
Acid	One-way ANCOVA	Sex	$F_{21,1}$ = 1.904; p = 0.182
Bitter	One-way ANOVA	-	$F_{22,1}$ = 13.819; p = 0.001
Umami	One-way ANCOVA	BMI	$F_{22,1}$ = 0.448; p = 0.510
B) Questionnaires			
FNS			
	One-way ANCOVA	VARSEEK score	$F_{23,1}$ = 2.75; p = 0.111
VARSEEK			
	One-way ANCOVA	FNS score	$F_{23,1}$ = 2.06; p = 0.165
IES			
Total	Independent Student's *t*-test	-	$t(24)$ = -2.45; p= 0.022
Subscale 1	One-way ANCOVA	GAD-7 and PHQ-9 scores	$F_{22,1}$ = 8.18; p = 0.009
Subscale 2	One-way ANCOVA	BMI, GAD-7 score	$F_{22,1}$ = 14.6; p = 0.001
Subscale 3	One-way ANCOVA	-	$F_{24,1}$ = 1.31; p = 0.264
BAQ			
Total[a]	Two-way ANOVA	-	Group effect: $F_{24,1}$ = 0.590; p = 0.450 Factor effect: $F_{72,3}$ = 28.881; p < 0.0005
Factor 1	One-way ANCOVA	Sex	$F_{23,1}$ = 0.732; p = 0.401
Factor 2	One-way ANOVA	-	$F_{24,1}$ = 1.12; p = 0.301
Factor 3	One-way ANOVA	-	$F_{24,1}$ = 1.08; p = 0.309
Factor 4	One-way ANOVA	-	$F_{24,1}$ = 0.215; p = 0.647

[a]Bonferroni correction.
[b]Survive a Bonferroni-Holm correction.
*Considered significant at p < 0.05;

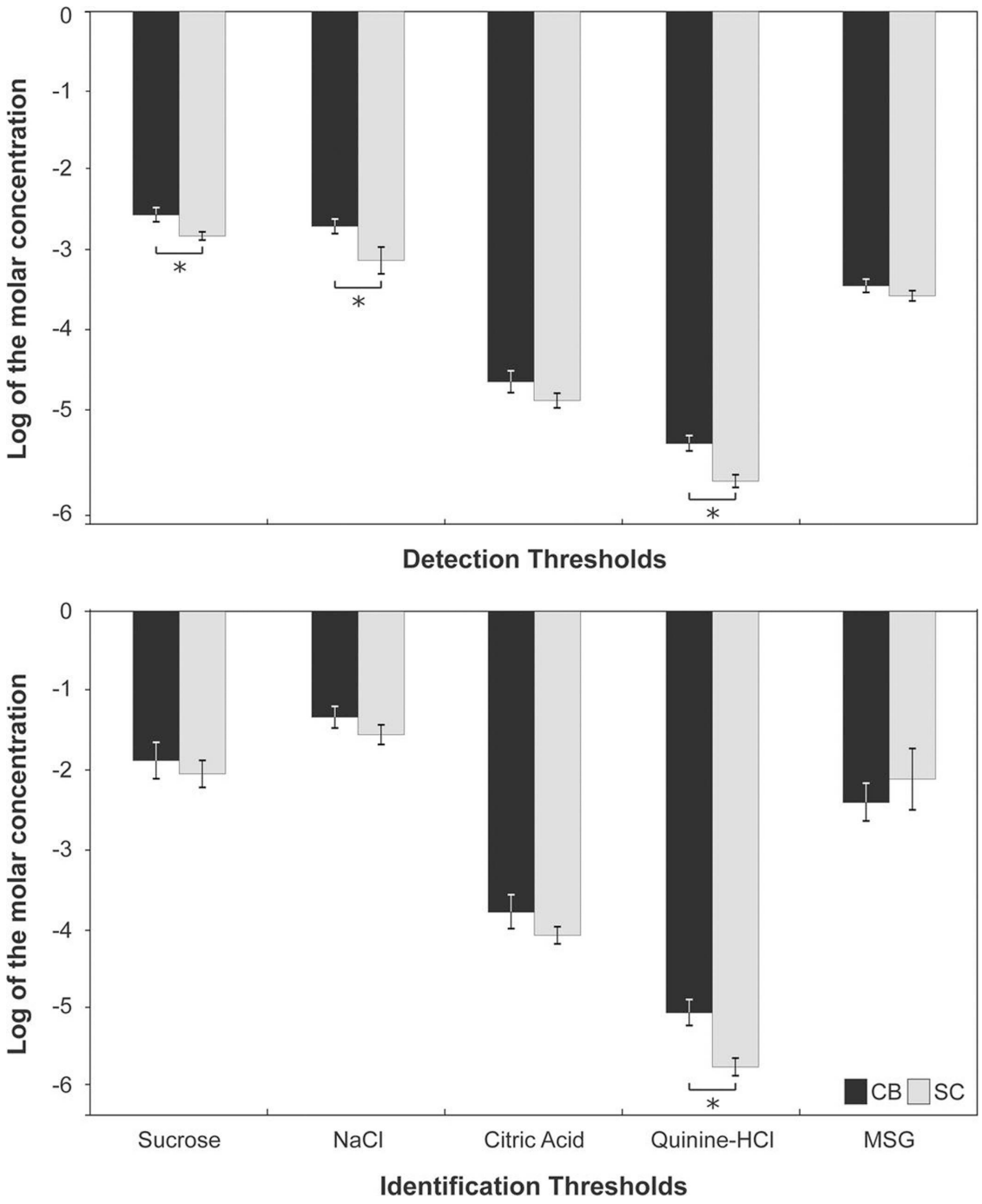

Figure 1 Bar charts showing mean ± standard error of the mean (SEM) gustatory detection and identification thresholds of the 5 basic taste qualities in congenitally blind (CB) and sighted control (SC) subjects. Thresholds are expressed in logarithmic values of the molar concentrations. The asterisks show significant group differences in taste thresholds at $p < 0.05$. Sighted individuals have a better general taste sensitivity compared with blind participants (group effect; $p < 0.05$). NaCl, sodium chloride; HCl, hydrochloride acid; MSG, monosodium glutamate.

Eating habits

Figure 2 shows the results on the "FNS" and "VARSEEK" scale. The analyses did not reveal significant group differences, neither in the fear of eating unfamiliar foods, nor in the search of variety in the diet.

As shown in Figure 3, blind subjects had a significantly higher total intuitive eating score. With respect to the results on the different subscales, the analyses revealed a significant group effect for the factors "unconditional permission to eat" and "eating for physical rather than emotional reasons" subscales. We did not find a group effect for the third subscale, which measures reliance on internal hunger and satiety cues.

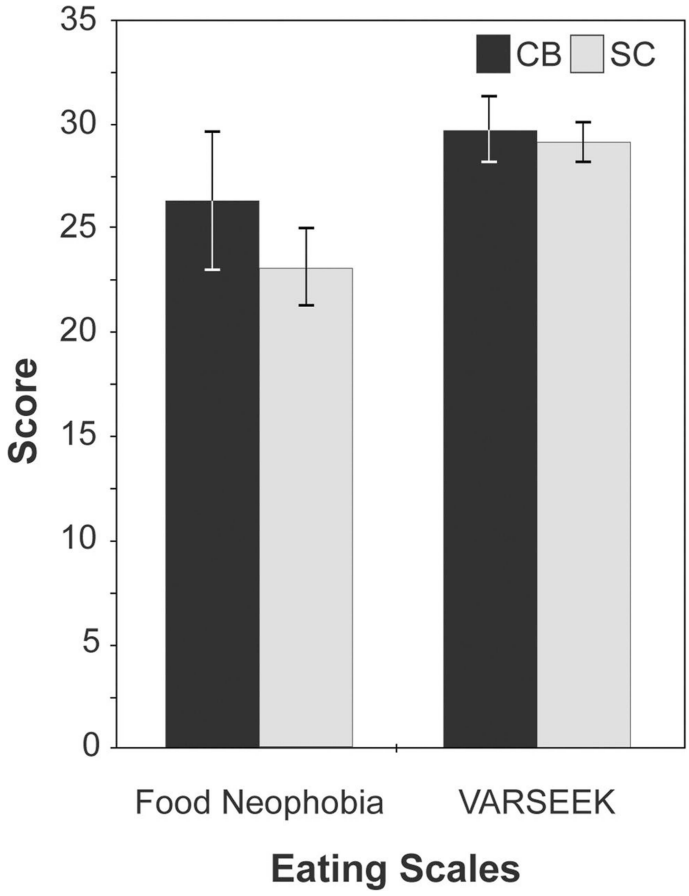

Figure 2 Bar charts showing mean ± SEM for food neophobia and food variety seeking tendency (VARSEEK) scores in congenitally blind (CB) and sighted control (SC) subjects.

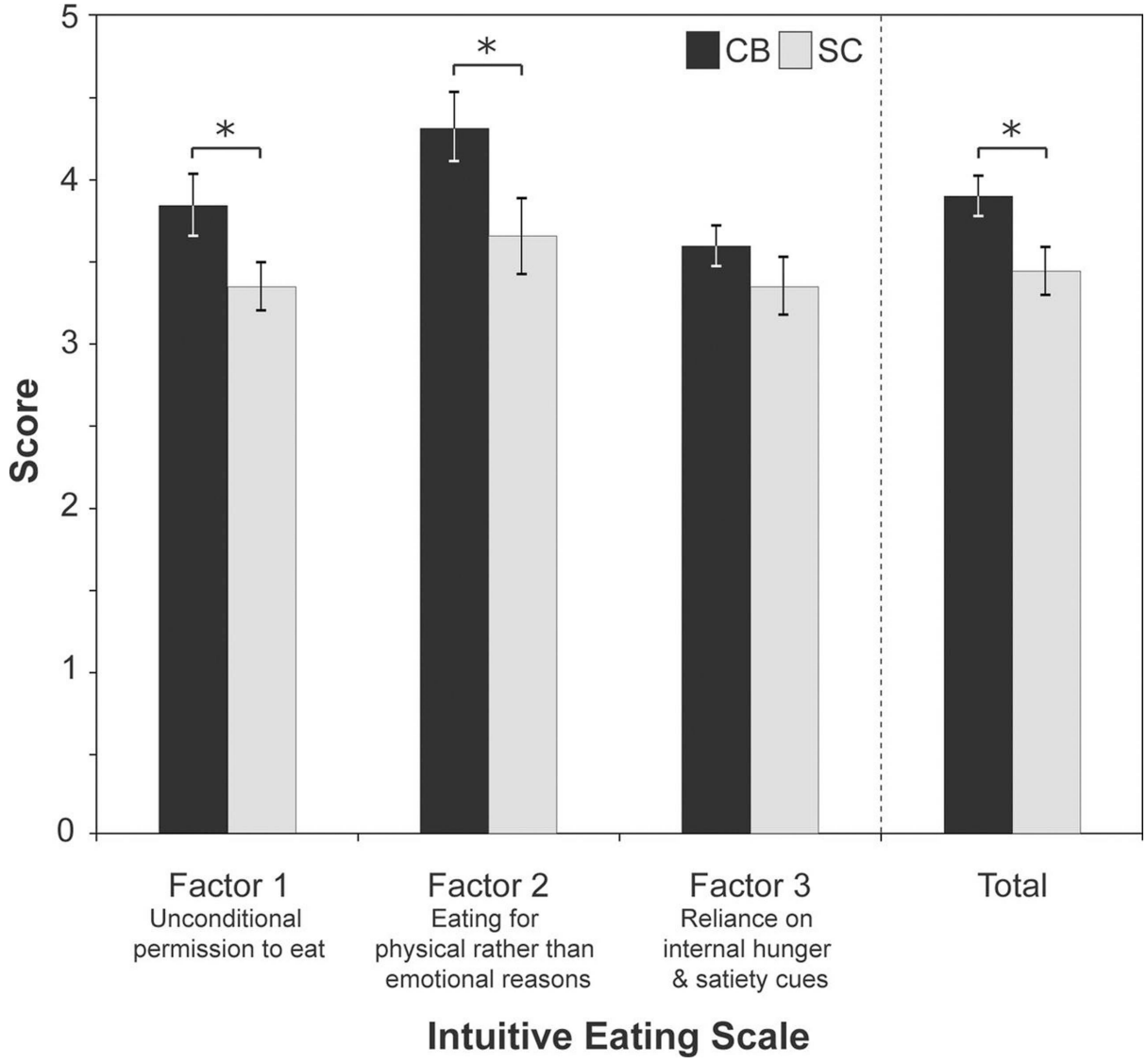

Figure 3 Bar charts showing mean ± SEM for the 3 factors' scores and mean total score of the IES in congenitally blind (CB) and sighted control (SC) subjects. The asterisks show significant results at $p < 0.05$. Blind participants allow themselves to eat more unconditionally (factor 1) and eat more for physical rather than for emotional reasons (factor 2) compared with sighted controls, which gives them a higher total mean intuitive eating score than sighted participants.

Finally, we did not find a group effect neither in the attentiveness to body cycles nor in the ability to detect and anticipate non-emotive changes and bodily reactions. The results of the BAQ are presented in Table 3.

Table 3. Results of the BAQ

Factors of the BAQ	Group	Mean and SEM
1. Note response and changes in the body	SC	22.1 ± 1.3
	CB	22.1 ± 2.0
2. Predict body reactions	SC	28.7 ± 1.7
	CB	23.9 ± 3.1
3. Sleep-wake cycle	SC	28.4 ± 1.4
	CB	24.0 ± 2.7
4. Onset of illness	SC	17.6 ± 1.1
	CB	15.7 ± 1.4

SEM, standard error of the mean.

Discussion

Our results show that blind subjects have a reduced taste sensitivity compared to their sighted counterparts, as demonstrated by their higher taste detection and identification thresholds for most of the 5 basic tastants. Interestingly, we found the smallest group difference for the identification of umami, a rather uncommon taste in western culture that is often confounded with salty. As predicted, we found that blind subjects adopt a better intuitive eating attitude than normal sighted controls. They refrain less and do not use emotional cues like sadness, loneliness or stress to indulge in abnormal eating behavior. Interestingly, blind and sighted subjects also share a similar attentiveness to body signals such as energy level. In contrast to our hypothesis, we did not find group differences in food neophobia and food variety seeking tendency.

Gustatory perception

Our finding of lower taste sensitivity in congenital blindness is in sharp contrast with the results found for the other sensory modalities where blind subjects often outperform their sighted counterparts. For instance, congenitally blind are better than sighted subjects in

discriminating pitch information (Gougoux *et al*., 2004) and in localizing sounds (Röder *et al*., 1999). Blind subjects are also better in tactile discrimination tasks (Van Boven *et al*., 2000; Chebat *et al.*, 2007; Wong *et al*., 2011), and in the detection (Cuevas *et al*., 2009; Beaulieu-Lefèbvre *et al.*, 2011) and identification of odorants (Rosenbluth *et al.*, 2000; Wakefield *et al.*, 2004; Cuevas *et al*., 2009; 2010; Rombaux *et al.*, 2010).

How then to explain this lower sensitivity in gustatory perception in blind subjects? In view of the earlier mentioned findings of superior performance of congenitally blind subjects in other non-visual sensory tasks, visual deprivation *per se* is unlikely to be the cause of their poorer performance. A more plausible explanation is that the reduced performance is training-related. Indeed, proficient Braille blind readers perform better than sighted controls in tactile discrimination tasks when testing the hands but not the face (Alary *et al.*, 2009; Wong *et al*., 2011). In addition, the blind's superior performance in pitch perception may be explained by the fact that they often use echolocation to detect, discriminate and identify distant objects (Kellogg, 1962; Teng *et al.*, 2012), a behavior that trains their pitch perception (Schenkman and Nilsson, 2011). Similarly, it has been suggested that blind individuals use much more odors as distal cues for wayfinding in urban environments (Koutsoklenis and Papadopoulos, 2011).

The gustatory system is also prone to training-induced plasticity. At the peripheral level, the turnover of taste receptors cells is only 10 days (Hill, 2004) which raises the intramodal plasticity potential. Previous studies have confirmed that taste identification thresholds vary according to tastant exposure (Kobayashi and Kennedy, 2002; Kobayashi *et al.*, 2006; Gonzalez *et al.*, 2008). For instance, when Americans/Europeans are submitted to a 1-week MSG-diet, their umami identification threshold lowers to levels similar to that of Japanese individuals who are daily exposed to high amounts of MSG (Kobayashi and Kennedy, 2002). This effect is reversed when the diet is changed back to normal (Kobayashi *et al.*, 2006). Unlike the other senses that are constantly bombarded by environmental sounds, visual stimuli and odors, exposure to gustatory stimuli depends to a large extent upon an individual's voluntary act of food ingestion. Although olfactory cues often incite tasting behavior, visual cues play an important role as well. For instance, when shopping in a food market, the color or shape of an unknown exotic fruit, the visual textural attributes of a rare cheese, and the packaging of a new type of spice may convince us to buy and taste these

products. As these visual cues are not accessible for blind individuals, they are exposed to a much more limited variety of taste stimuli, which may explain their lower taste sensitivity. Blind customers plan in advance their list of groceries rather than buying spontaneously in grocery shops or markets. Practical issues such as blindness-related obstacles during shopping, preparing food and eating out (Bilyk *et al.*, 2009) reduce the accessibility to a large variety of food, and therefore food exposure, despite a willingness to try and diversify their diet, as indicated by their normal food neophobia and variety seeking tendency scores. These limitations could be partly overcome by improving help and access to food products in supermarkets (for a pilot project, see Kulyukin *et al.*, 2008), extending European Braille packaging rules for pharmaceutical products to food items, providing well documented Web sites to shop online, and improving security in the kitchen environment (Kutintara *et al.*, 2013). This would strongly increase the quality and diversity of eating experience in the visually impaired.

Eating habits

Food preferences have a strong impact on body shape. Adaptive eating, as opposed to maladaptive eating which leads to eating disorders, is described as a positive eating behavior that is triggered by physiological hunger and satiety cues rather than by external and emotional cues (Tylka, 2006). Our results show that blind subjects have eating habits advantages over the sighted. The higher scores on the IES in blind participants are in line with findings of increased body satisfaction (Tylka, 2006), specifically in female blind subjects (Baker *et al.*, 1998; Ashikali and Dittmar, 2010). As blind subjects are less exposed to the slim-body beauty ideal that is relentlessly promoted by the visual media, it may be hypothesized that they are less concerned about their body contour, thereby allowing themselves to eat without restraint (factor 1). It is important to stress that "eating without restraint" does not necessarily mean binge eating but rather eating *ad libitum*, that is, until real satiation is reached. An advantage of engaging less in dietary regimes is a reduced risk of confusing ambiguous hunger/satiety signals with emotional agitation and distress (Herman *et al.*, 1987). This explains why blind subjects eat more for physical than for emotional reasons.

Our data do not support our hypotheses that blind subjects would be more neophobic and score lower on food variety-seeking. Unlike deaf-blind children who are strongly

neophobic towards food (Luiselli, 1993), congenitally blind adults are not afraid to try unfamiliar foods and are seeking as much variety in their diet as do sighted control subjects. Besides the age difference between the blind subjects in the latter study and ours, an explanation for this difference may be that blind adults have overcome their fear for novel foods, as they have learned that trying unknown foods can also be positively rewarding.

Conclusion

We showed that congenitally blind subjects exhibit lower taste sensitivity than sighted controls. Further research is needed to test whether this reduced gustatory sensitivity is caused by a less diversified diet, caused by various difficulties that blind individuals encounter when shopping and preparing food. Our results on eating habits also encourage further research in improving food accessibility for the visually impaired. Giving that eating is an important aspect of quality-of-life, this could have a beneficial impact on the well-being of blind individuals.

Supplementary material

Supplementary material can be found at:
http://chemse.oxfordjournals.org/content/suppl/2013/05/09/bjt021.DC1

Supplementary Table 1. Summary of the statistical analysis

	Tests chosen (ordered)	Dependant variable(s)	Covariates included	Results
A) Taste sensitivity				
General				
	Three-way ANCOVA	Molar values of the individual taste thresholds (detection and identification)	Age, Sex, BMI, PTC sensitivity	Dependant variable not normally distributed
	Three-way ANCOVA	Logarithmic values of the individual taste thresholds (detection and identification)	Age, Sex, BMI, PTC sensitivity	No significant covariate
	Three-way ANOVA		-	
Detection				
Sweet	One-way ANCOVA	Logarithmic value of the individual threshold	Age, Sex, BMI, PTC sensitivity	Violation of the postulate of homogeneity of regression
	Independent Student's *t*-test		-	
Salty	One-way ANCOVA		Age, Sex, BMI	Violation of the postulate of homogeneity of regression
	Independent Student's *t*-test		-	
Acid	One-way ANCOVA		Age, Sex, BMI	Violation of the postulate of homogeneity of regression
	Independent Student's *t*-test		-	
Bitter	One-way ANCOVA		Age, Sex, BMI, PTC sensitivity	Violation of the postulate of homogeneity of regression
	Independent Student's *t*-test		-	
Umami	One-way ANCOVA		Age, Sex, BMI	Age and Sex were not significant covariates
	One-way ANCOVA		BMI	
Identification			-	
Sweet	One-way ANCOVA		Age, Sex, BMI	No significant covariate
	One-way ANOVA		-	
Salty	One-way ANCOVA		Age, Sex, BMI	Violation of the postulate of homogeneity of regression
	Independent Student's *t*-test		-	
Acid	One-way ANCOVA		Age, Sex, BMI	Age and BMI were not significant covariates
	One-way ANCOVA		Sex	
Bitter	One-way ANCOVA		Age, Sex, BMI, PTC sensitivity	No significant covariate
	One-way ANOVA		-	
Umami	One-way ANCOVA		Age, Sex, BMI	Age and Sex were not significant covariates
	One-way ANCOVA		BMI	

B) Questionnaires

FNS				
	One-way ANCOVA	FNS individual score	Age, GAD-7 and VARSEEK scores	Age and GAD-7 score were not a significant covariates
	One-way ANCOVA		VARSEEK score	
VARSEEK				
	One-way ANCOVA	VARSEEK individual score	Age and FNS score	
	One-way ANCOVA		FNS score	
IES				
Total	One-way ANCOVA	Mean IES individual score	BMI, GAD-7 and PHQ-9 scores	Violation of the postulate of homogeneity of regression
	Independent Student's *t*-test		-	
Subscale 1	One-way ANCOVA	IES's subscale 1 individual score	BMI, GAD-7 and PHQ-9 scores	BMI was not a significant covariate
	One-way ANCOVA		GAD-7 and PHQ-9 scores	
Subscale 2	One-way ANCOVA	IES's subscale 2 individual score	BMI, GAD-7 and PHQ-9 scores	PHQ-9 score was not a significant covariate
	One-way ANCOVA		BMI, GAD-7 score	
Subscale 3	One-way ANCOVA	IES's subscale 3 individual score	BMI, GAD-7 and PHQ-9 scores	No significant covariate
	One-way ANCOVA		-	
BAQ				
Total	Two-way ANCOVA	individual scores (F1-F4)	Age, Sex	No significant covariate
	Two-way ANOVA		-	
Factor 1	One-way ANCOVA	BAQ's F1 individual score	Age, Sex	Age was not a significant covariate
	One-way ANCOVA		Sex	
Factor 2	One-way ANCOVA	BAQ's F2 individual score	Age, Sex	No significant covariate
	One-way ANOVA		-	
Factor 3	One-way ANCOVA	BAQ's F3 individual score	Age, Sex	No significant covariate
	One-way ANOVA		-	
Factor 4	One-way ANCOVA	BAQ's F4 individual score	Age, Sex	No significant covariate
	One-way ANOVA		-	

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Article 2

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Superior orthonasal but not retronasal olfactory skills in congenital blindness

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Abstract

Sight is undoubtedly important for finding and appreciating food, and cooking. Blind individuals are strongly impaired in finding food, limiting the variety of flavours they are exposed to. We have shown before that compared to sighted controls, congenitally blind individuals have enhanced olfactory but reduced taste perception. In this study we tested the hypothesis that congenitally blind subjects have enhanced orthonasal but not retronasal olfactory skills. Twelve congenitally blind and 14 sighted control subjects, matched in age, gender and body mass index, were asked to identify odours using grocery-available food powders. Results showed that blind subjects were significantly faster and tended to be better at identifying odours presented orthonasally. This was not the case when odorants were presented retronasally. We also found a significant group x route interaction, showing that although both groups performed better for retronasally compared to orthonasally presented odours, this gain was less pronounced for blind subjects. Finally, our data revealed that blind subjects were more familiar with the orthonasal odorants and used the retronasal odorants less often for cooking than their sighted counterparts. These results confirm that orthonasal but not retronasal olfactory perception is enhanced in congenital blindness, a result that is concordant with the reduced food variety exposure in this group.

Keywords: orthonasal, retronasal, olfaction, blindness, plasticity.

Introduction

Chemicals can reach the nasal epithelium using the orthonasal or the retronasal route. The orthonasal route brings odorants from the environment to the nasal cavity via the nostrils during inspiration (or sniffing). The retronasal route, on the other hand, conveys odorants from the mouth to the nasal epithelium via the nasopharynx during exhalation. Although molecules can reach the nasal epithelium using these two routes, the associated perceptions often differ. For example, while freshly brewed coffee has a delightful perfume, its flavour may seem comparingly disappointing. On the contrary, a cheese like Époisses with the repulsive smell of sweaty shoes has a delicious flavour once inside the mouth. This is referred to as the "olfactory duality" of odorants referred to the mouth (internal body) or the external world [1].

There is strong evidence that vision can influence orthonasal olfaction [2-5], taste [6, 7] and flavour [8-13] perception. However, the impact of vision on retronasal olfaction alone remains largely unexplored. A study by Koza and collaborators (2005) showed that color increases intensity ratings when odorants are delivered orthonasally, but has the opposite effect following retronasal delivery [14]. These findings suggest that vision affects the ortho- and retronasal pathways differently, supporting the relative independence of the two routes.

Research from our and other laboratories has shown that visual deprivation from birth leads to higher odour awareness [15], better orthonasal detection, discrimination and/or identification skills [15-19], but lower taste abilities [20] when compared to a matched control group of sighted subjects. We suggested that the reduced taste abilities are related to various blindness-related obstacles when shopping, cooking and finding foods [20, 21], all of which contribute to underexpose the tongue to a variety of taste and flavour stimuli. The objective of the current study was to test the hypothesis that congenitally blind subjects have increased orthonasal together with decreased retronasal odour identification skills. As the identification of individual ingredients is necessary for preparing a dish, we further hypothesized that blind individuals would use the (retronasal) odorants less frequently than sighted when cooking.

Material and Methods

Participants

A total of 12 congenitally blind (4 females; [mean ± SEM] 42 ± 4 years; body mass index (BMI): 25.2 ± 1.5 kg/m2) and 14 sighted control (5 females; 40 ± 4 years; BMI: 23.6 ±

0.8 kg/m2) subjects participated in the study. Table 1 summarizes the demographic data and causes of blindness. All participants were asked to avoid eating strong foods (e.g. chili, garlic) 24h before the experiment, not to use perfume the day of the experiment and refrain from eating, drinking (except water) and chewing gum at least 1h prior to testing. This study was conducted in accordance with the Declaration of Helsinki. The research ethics committee of the Capital region of Denmark approved the study [H-2-2013-058] and all subjects gave informed and written consent prior testing.

Table 1. Demographic data of blind participants.

Sex	Age (y)	Education (y)	Etiology of blindness	Onset of blindness	Residual vision	Cooking frequency
F	26	16	Retinopathy of prematurity	Birth	None	Rarely
F	31	13	Retinopathy of prematurity	Birth	None	Once a day
F	45	15	Retinopathy of prematurity	Birth	Shapes (OS)	Rarely
F	64	10	Retinopathy of prematurity	Birth	None	Rarely
M	25	12	Retinopathy of prematurity	Birth	None	Rarely
M	29	13	Retinopathy of prematurity	Birth	None	Rarely
M	38	17	Optic nerve atrophy	Birth	None	Few times a week
M	39	12	Unknown	Birth	None	Few times a month
M	42	16	Retinopathy of prematurity	Birth	Light	Few times a day
M	45	15	Meningitis	1 year	Light, shapes	Few times a day
M	53	14	Retinopathy of prematurity	Birth	None	Few times a month
M	61	16	Retinopathy of prematurity	Birth	None	Few times a week

F, female; M, male; y, years; OS, left eye.

Testing procedure

Grocery store condiments and other food items available or grinded into powder form (e.g. dried vegetables, candies, spices, etc.) were used as olfactory stimuli, following the protocol of Heilman and colleagues (2002). As the current study investigated differences between two normosmic populations, we extended the original 20 stimuli to 38 and assigned one half to orthonasal and the other half to the retronasal set (Table 2), based upon their smell and taste intensity scores that were assessed in a pilot study.

All testing was carried out with participants blindfolded. We first tested orthonasal identification skills by placing the plastic vial containing the food powder 5 cm below the

participant's nose. The subject was asked to take two normal breaths and identify as fast as possible the odorant (free orthonasal identification) while the experimenter was recording the response time using a stopwatch. Following the free identification, the experimenter verbally provided 4 possible choices and the participant had to select one of them (multiple-choice orthonasal identification). The participant was then asked whether he/she was familiar with the odour (yes/no) and if he/she has used it for cooking (yes/no). Total free and multiple choice identification scores were obtained by calculating the percentage of correct answers. For each subject, we also calculated the percentage of orthonasal stimuli that were familiar and used for cooking.

Table 2. Orthonasal and retronasal stimuli.

	Orthonasal Target item	Distractor items	Retronasal Target item	Distractor items
1	Vanilla	Cherry, Banana, Honey	Ginger	Mustard, Paprika, Curry
2	Onion	Chives, Salami, Smoked Ham	Lemon	Grapefruit, Sour Cherry, Redcurrant
3	Mushrooms	Bread, Fish, White Wine	Bread	Sauerkraut, Pizza, Garlic
4	Paprika	Ginger, Curry, Mustard	Milk	Vanilla, Banana, Coconut
5	Smoked Ham*	Fish, Bread, Chives	Strawberry	Apple, Redcurrant, Tangerine
6	Cloves	Anise, Caraway, Dill	Orange	Raspberry, Strawberry, Cherry
7	Garlic	Ham, Chives, Celery	Cocoa	Caramel, Muscat, Juniper
8	Nutmeg	Cinnamon, Coffee, Cocoa	Coffee	Muscat, Cinnamon, Cocoa
9	Curry	Mustard, Cheese, Cucumber	Cinnamon	Caramel, Cocoa, Honey
10	Raspberry	Peach, Pineapple, White Grapes	Peach	Raspberry, Pineapple, Grapes
11	Parsley	Chives, Carrots, Celery	Banana	Milk, Vanilla, Coconut
12	Caraway	Cloves, Anise, Dill	Apple	Strawberry, Redcurrant, Tangerine
13	Juniper	Caramel, Muscat, Cocoa	(Sour) Cherry	Grapefruit, Redcurrant, Lemon
14	Chives	Celery, Parsley, Carrots	Caramel	Cocoa, Cinnamon, Honey
15	Fish	Smoked Ham, Bread, Chives	Cheese	Curry, Cucumber, Mustard
16	Anise	Cloves, Caraway, Dill	Tangerine	Apple, Redcurrant, Strawberry
17	Dill	Caraway, Anise, Cloves	Pineapple	Peach, Grapes, Raspberry
18	Grapes	Peach, Pineapple, Raspberry	Pizza	Bread, Garlic, Sauerkraut
19	Coconut	Vanilla, Milk, Banana	Celery	Chives, Parsley, Carrots

Word inside parenthesis was not required to earn a point for free identification. *Subjects who identified either "smoked" or "ham" got half a point for free identification.

After a short 10-minute break, we tested retronasal identification skills. Two mL of stimulus powder was placed on the tongue using a teaspoon, while the subject had his/her nostrils occluded. After stimulus delivery, the participant was asked to close his/her mouth, unblock his/her nostrils, breathe normally and identify the odorant (free retronasal

identification) while the experimenter recorded his/her response time. We calculated the percentage of multiple-choice retronasal identification as described above. The participant was again asked about odour familiarity (yes/no) and use of the odour in cooking (yes/no). Participants rinsed their mouth following each stimulus presentation. One blind subject was not exposed to bread, milk, cocoa, caramel and cheese because he was allergic to these compounds. We also calculated the percentage of retronasal stimuli that were familiar and used for cooking for each participant.

Finally, all subjects were asked to rate their general cooking frequency on a 6-point category scale (never, rarely, few times a month, few times a week, once a day, few times a day). Cooking was defined as transforming food. For example, preparing an omelet was considered as cooking but using a microwave to warm up a dish was not.

Analysis

Results were analysed using SPSS 21.0 (SPSS Inc, Chicago, Illinois). To test for group differences in olfactory performance or subjective experience with odours, we conducted a repeated ANCOVA with route (ortho vs. retro) as within-subject factor and group (blind vs. sighted) as between-subject factor with each of the following independent variables: free and multiple-choice identification scores, response times (for free identification) as well as the proportion of stimuli familiar to the subjects and used for cooking. Age, gender, body mass index (BMI), familiarity, usage of odorants for cooking and/or cooking frequency were considered as possible covariates. Finally, to test for group difference in cooking frequency, we conducted a Mann-Whitney U-test.

Both ortho- and retronasal olfactory functions vary as a function of gender – with women being better than men [22, 23] - and slowly decline with age [22, 24]. We hypothesized that familiarity with the stimuli and/or their use for cooking would give an advantage to olfactory skills. As we had a specific hypothesis about group advantages for the identification scores, usage for cooking and cooking frequency, we used one-tailed tests. We applied two-tailed tests for the remaining dependent variables (odour familiarity and reaction times). We used a Mann-Whitney U-test in case of non-normal distribution of the data or a t-test in case of violation of the postulate of homogeneity of regression [25]. Significance level

for all statistical tests was fixed at $p < 0.05$, applying a Bonferroni correction for multiple tests.

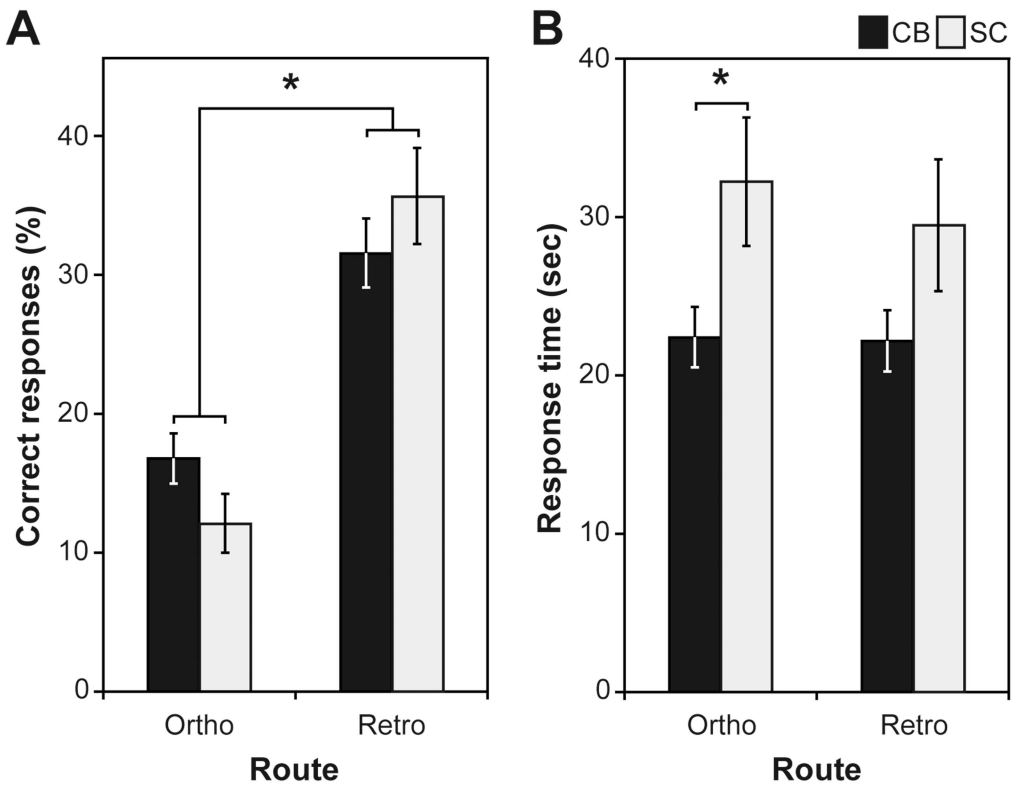

Fig. 1. Orthonasal and retronasal odour free identification. Data are presented as mean ± standard error of the mean (SEM). A. Significant group x route interaction indicating better and worse performances respectively for orthonasal and retronasal odour free identification in congenitally blind (CB) compared to sighted controls (SC). B. Shorter response time in CB compared to sighted controls SC during the free identification task. *Significant at $p < 0.05$.

Results

Fig. 1A illustrates the mean orthonasal and retronasal free identification scores. Gender was the only significant covariate (free $p = 0.013$; multiple-choice $p = 0.036$) that had an effect on the odour identification skills. As expected, we observed a significant group x route interaction ($F(23,1) = 4.696$; $p = 0.041$), a trend towards a route effect ($F(23,1) = 4.026$; $p = 0.057$) and no group effect ($F(23,1) = 0.027$; $p = 0.871$). Whereas blind participants scored higher than sighted controls during orthonasal testing, they scored lower than the controls when tested retronasally. The group difference favouring the blind in orthonasal free identification almost reached significance ($p = 0.057$). For the multiple-choice identification

scores, multivariate ANCOVA revealed only a trend towards a route effect ($F(23,1) = 3.139$; $p = 0.090$), no group effect ($F(23,1) = 0.614$; $p = 0.441$) and no group x route interaction ($F(23,1) = 0.400$; $p = 0.533$; supplementary material). For both free and multiple-choice identification, retronasal odour identification tended to be easier than orthonasal odour identification.

Fig. 1B illustrates the mean response times for both ortho- and retronasal free identification. Blind subjects were significantly faster than sighted controls in the orthonasal ($t(24,1) = 2.189$; $p = 0.042$) but not in the retronasal ($U(24, 1) = 64.00$; $p = 0.322$) task.

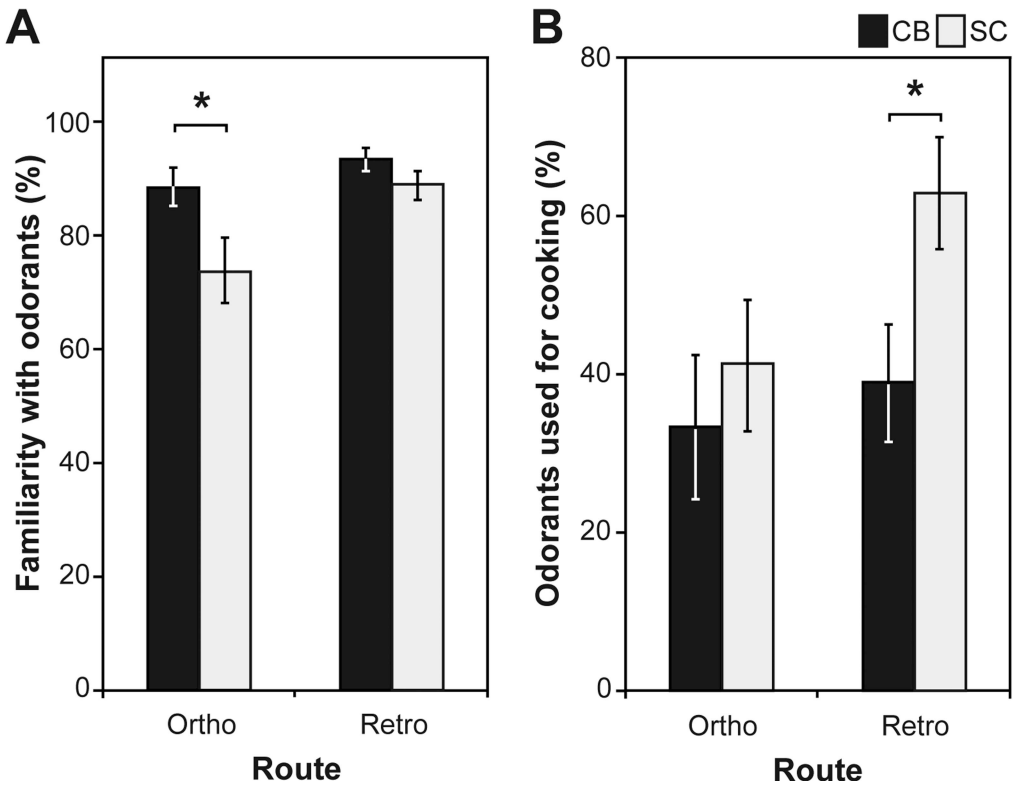

Fig. 2. Subjective experience with odours. Data are presented as mean ± SEM. A. Congenitally blind (CB) are more familiar with the orthonasal odours and B. use less retronasal odours for cooking than sighted controls (SC). *Significant at $p < 0.05$.

Fig. 2 illustrates that blind subjects were more familiar with the orthonasal odours compared to sighted controls ($F(24,1) = 4.663$; $p = 0.041$). There was no group difference for the retronasal stimuli ($U(24, 1) = 60.50$; $p = 0.231$). In line with our hypothesis, congenitally blind subjects also cooked less often with the odorants used for the retronasal testing ($F(24,1)$

= 4.679; p = 0.021), whereas there was no such difference for the orthonasal odours (U(24, 1) = 73.00; p = 0.595).

Finally, congenitally blind individuals cooked less often than sighted controls subjects (U(24, 1) = 49.50; p = 0.038). Whereas more than half of the blind subjects (58%) indicated cooking a few times a month or less, half of the sighted participants (50%) reported cooking at least once a day.

Discussion

The present data show that congenitally blind subjects are better than sighted controls at identifying odorants presented via the orthonasal but not via the retronasal route. In particular, blind subjects were faster in recognizing orthonasally presented odours and they showed a strong trend for better performance on the orthonasal free identification test. Importantly, we did find a significant route x group interaction, supporting our hypothesis that congenitally blind have enhanced orthonasal olfactory abilities but lose this behavioral advantage when smelling retronasally. Moreover, whereas blind subjects were more familiar with the orthonasal odorants, they used the retronasal odorants less for cooking, offering a possible explanation for their olfactory performances.

The olfactory system is strongly prone to both short and long-term experience-induced plasticity at cellular, synaptic and network level [26]. In the absence of vision, individuals will rely more strongly on orthonasal olfaction, as it becomes the second most important telereceptive sense after audition. Odours can be used as distal cues for wayfinding [27-29] and for social interactions with others [15, 30, 31]. Smelling the environment through the nostrils can provide representations of the actions and emotions of others [32-34]. For example, inhaling the smell of grilled meat and burning charcoal may inform that the neighbours are barbecuing. Similarly, smelling body odours enables kin and emotion recognition [35-37]. By relying more strongly on their orthonasal sense of smell, blind individuals hence come to better understand and interact with the external world [15-19]. This may also explain the increased volume of the olfactory bulb in congenitally blind individuals [19] and their stronger blood oxygenation-level dependent (BOLD) response to odorant stimuli in brain areas involved in orthonasal olfactory perception, like the amygdala, hippocampus and orbitofrontal cortex [35, 38-39]. Our results are thus in line with a variety of

studies showing the superiority of congenitally blind individuals in performing orthonasal olfactory tasks.

Whereas our orthonasal sense of smell receives permanent input by a constant flow of various odours from our surrounding environment, retronasal olfactory perception relies upon the act of eating. Eating implies the search for foods, the decision of what and how much to eat and, importantly, the act of preparing food. Vision largely influences food searching and eating behaviour. Not only does the dorsal visual system enable foraging but the ventral visual stream allows rapid food identification and palatability evaluation. Although both dorsal and ventral streams remain functionally intact in the congenitally blind brain and are recruited through the remaining sensory modalities [40-42], navigational skills are impaired [43]. In modern Western urban societies, food identification prior to ingestion has become more challenging, as most palatable items are packaged in such a way that its excludes olfactory or haptic exploration that may give cues about the identity of the food product. As a result, when blind subjects shop in grocery stores, they largely depend upon a third person to locate and identify food items [21, 44]. Since blind persons' decisions to buy foods are not influenced by visual attractiveness, they buy less spontaneously and very often limit themselves to foods that they have indicated on their pre-prepared Braille grocery shopping list. This reduces the possibility of discovering new food products, as is often the case for sighted individuals. More importantly, meal preparation is also difficult without vision. Sharp knifes, hot stoves and even opened doors of high cabinets are sources of multiple injuries for the visually impaired [45]. When eating, external visual cues, like the quantity of food left in the plate [46, 47], visual characteristics of the food and dishes [48-51], facial expressions and body shapes of the people with whom we eat [52], constantly influence our intake of foods. Without these cues, blind people eat slower [46], consume more intuitively and restrain less than sighted subjects [20]. We suggest that these difficulties in food searching and eating behaviour not only have downside effects on taste perception [20] but also on retronasal olfactory abilities, as demonstrated in this study.

Conclusion

In conclusion, our results indicate that the olfactory advantage of congenitally blind over sighted controls largely depends upon the route of stimulation. Whereas blind subjects

are better at the orthonasal identification of food odours, they lose their superiority when palatable odours are smelled retronasally through the pharynx. Results on familiarity with foods and their usage for cooking were concordant with perceptual differences, supporting experience-dependent olfactory plasticity. Our results encourage further research in improving access to foods, meal preparation and gastronomy for the visually impaired. As cooking and eating are social activities that largely influence quality-of-life, this could promote independence and positively affect the well-being of people suffering from visual impairments.

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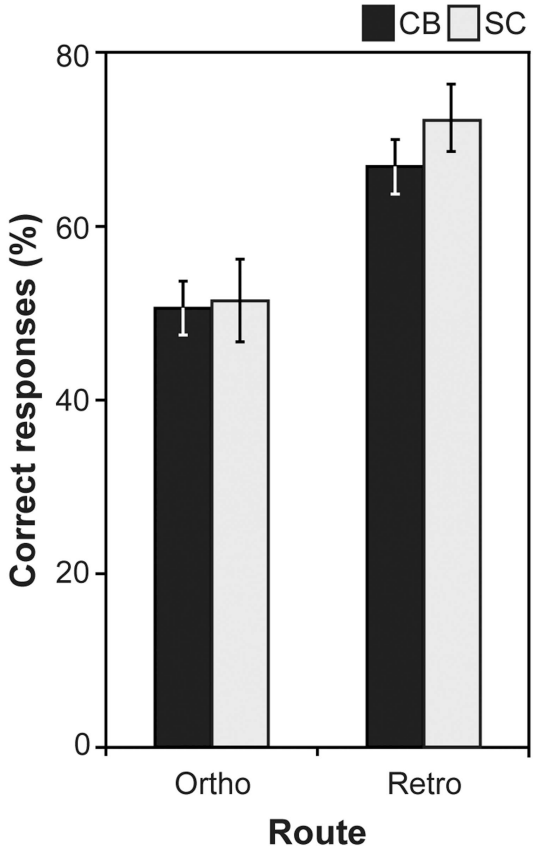
Supporting Information

The forced-choice odour identification skills are illustrated in S1 Fig.



S1_Fig. Orthonasal and retronasal odour identification. Data are presented as mean ± SEM. Congenitally blind (CB) perform equally well than sighted control (SC) subjects at identifying odours using a multiple-choice paradigm.

Article 3

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Neural correlates of taste perception in congenital blindness

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Abstract

Sight is undoubtedly important for the perception and the assessment of the palatability of tastants. Although many studies have addressed the consequences of visual impairments on food selection, feeding behaviour, eating habits and taste perception, nothing is known about the neural correlates of gustation in blindness. In the current study we examined brain responses during gustation using functional magnetic resonance imaging (fMRI). We scanned 9 congenitally blind and 14 blindfolded sighted control subjects, matched in age, gender and body mass index (BMI), while they made judgements of either the intensity or the (un)pleasantness of different tastes (sweet, bitter) or artificial saliva that were delivered intra-orally. The fMRI data indicated that during gustation, congenitally blind individuals activate less strongly the primary taste cortex (right posterior insula and overlying Rolandic operculum) and the hypothalamus. In sharp contrast with results of multiple other sensory processing studies in congenitally blind subjects, including touch, audition and smell, the occipital cortex was not recruited during taste processing, suggesting the absence of taste-related compensatory crossmodal responses in the occipital cortex. These results underscore our earlier behavioral demonstration that congenital blind subjects have a lower gustatory sensitivity compared to normal sighted individuals. We hypothesized that due to an underexposure to a variety of tastants, training-induced crossmodal sensory plasticity to gustatory stimulation does not occur in blind subjects.

Keywords: gustation, visually impaired, crossmodal plasticity, fMRI.

1. Introduction

The importance of sight for taste perception is highlighted by the popular French saying "Nous goûtons avec les yeux" (We taste with our eyes). Unlike smell, touch and audition that sense foods both prior (e.g. orthonasal olfaction) and during (e.g. retronasal olfaction) ingestion, vision is the sense that solely (and naturally) perceives food outside the body. On the other hand, taste perception is restricted to the internal experience of food inside the mouth (e.g. sweet, bitter) or digestive tract (e.g. visceral distension). Therefore, the sight of foods builds a mindset of expectations about the internal experience of the foods we eat. In a single eye blink, we gather information about the availability, location, identity, palatability, flavor, texture, intensity, pleasantness, nutritive and energy contents of the food object. Through learning, vision powerfully sharpens our expectations about a food and prepares the body to respond accordingly (Feldman & Richardson, 1986; Powley, 2000; Crum *et al*., 2011). At the brain level, sight modulates the gustatory cortex to respond to tastants according to expectations (Nitschke *et al*., 2006; Veldhuizen *et al*., 2011). Stimulus-specific representations can also be activated before the experience of the stimulus. For example, seeing taste-related words (compared to non-taste-words) or pictures of foods (compared to non-foods) produces activity in the hedonic-hunger network, that includes visual and reward areas together with primary (insula and overlying operculum) and secondary (orbitofrontal) taste cortices (Barros-Locertales *et al*., 2011; review in Van der Laan *et al*., 2011).

It is not surprising that vision also affects the perception of tastants and flavors (Delwiche, 2012). For example, adding color to a drink or a food can increase or lower a person's ability to discriminate or identify tastants or flavors, even if he/she is instructed that color only contains non-relevant information (Zampini *et al*., 2007; Levitan *et al*., 2008; Spence *et al*., 2010; reviews in Verhagen & Engelen, 2006; Zampini & Spence, 2012). Crossmodal influences of vision on taste perception go even beyond the characteristics of the consumed food and extend to the visual aspects of the cutlery (Harrar & Spence, 2013), dishes (Harrar *et al*., 2011), ambiance lighting (Wheatley, 1973) and social cues (e.g. facial expressions and body shapes of dining partners; Barthomeuf *et al*., 2010), suggesting that eating and drinking are complex and multisensory rewarding experiences in which context plays an important role.

Visual cues also play an important role in food consumption, especially when one is hungry. The physiological state of hunger or satiety, coded by the gustatory system, directs visual attention towards relevant visual stimuli in an alliesthesic fashion. For example, hungry sighted participants perform worse that sated controls in attentional tasks that require ignoring food items (Piech *et al*., 2010). Furthermore, when visual input is blocked, e.g. by wearing a blindfold, participants eat nearly 20% less (Linné *et al*., 2002).

What are the effects of the (congenital) absence of vision on the development of the taste system? People who are blind from birth experience numerous obstacles related to selection and access of food products, as well as in the preparation of meals (Bilyk *et al*., 2011). For example, during grocery shopping, many blind individuals rely on a memorised list of food items. This is in sharp contrast with sighted persons whose food-choice is to a large extent based upon the appealing visual aspects of foods such as their color, shape, label or packaging. Blind subjects also eat slower compared to (blindfolded or not) sighted subjects (Linné *et al*., 2002). We recently provided evidence that congenitally blind individuals have higher taste detection and identification thresholds (Gagnon *et al*., 2013), a result that contrasts sharply with their increased sensitivity to touch, sound and odour (review in Kupers & Ptito, 2014). We further showed that blind subjects have a better intuitive eating attitude compared to sighted, meaning that they rely more strongly on their physiological feeling of hunger rather than on external and situational cues, when deciding what and how much to eat (Gagnon *et al*., 2013; 2014). We here test whether the reduced taste sensitivity in congenitally blind subjects is reflected at the neuronal level by attenuated blood oxygenation-level dependent (BOLD) responses in the primary and/or secondary taste cortices. Based on studies showing that blind individuals are less exposed to various tastants (Bilyk et al., 2009) and that occipital activation by non-visual sensory stimulation in blind subjects is training induced (Kupers & Ptito, 2014), we hypothesized that they will activate less strongly their taste cortex and will not recruit their occipital cortex in a gustatory task.

2. Methods

2.1. Participants

Twelve congenitally blind (7 females) and 14 blindfolded sighted control (5 females) subjects participated in this study. All participants were right-handed, as assessed with the

Edinburgh Handedness Inventory (Oldfield, 1971). Blind participants were recruited through either the Nazareth & Louis Braille Institute, the MAB-Mackay center and/or the Canadian National Institute for the Blind. Demographic data of the blind subjects are given in Table 1. Prior to the fMRI study, all participants were first screened for olfactory impairments using the Sniffin' Sticks screening 12-test battery (Hummel *et al.*, 2001), and they were also familiarized with the gustometer. This led to the rejection of one blind anosmic male and one blind female who was unable to perform the training task. All other participants scored higher than 8 on the smell identification test. An additional blind female participant was removed from the fMRI data analysis because of head movements during scanning. The resulting blind (5/9 females; [mean ± SEM] age: 45 ± 5 y; body mass index (BMI): 27.5 ± 1.4 kg/m^2) and sighted (6/14 females; age: 39 ± 4 y; BMI: 29.0 ± 1.9 kg/m^2) groups were matched for age, gender and BMI. The local Ethics Research Committees of the Centre de Recherche Interdisciplinaire en Réadaptation [CRIR 838-0413] and of the Regroupement de Neuroimagerie du Québec [CMER RNQ 10-11-027] approved the experimental protocol and all participants gave their written informed consent prior testing.

Table 1. Demographic datas of blind participants.

Sex	Age (y)	BMI (kg/m^2)	Etiology of blindness	Onset of blindness	Residual vision
F	47	27.1	Retinopathy of prematurity	Birth	Light
F*	43	47.2	Retinopathy of prematurity	2 months	No
F*	50	26.2	Congenital cataracts and coloboma	Birth	No
M	44	22.3	Retinopathy of prematurity	Birth	No
F	57	24.1	Retinopathy of prematurity	Birth	No (1 eye prosthesis)
M	56	28.4	Optic atrophy	2 months	No
F	32	23.5	Retinopathy of prematurity	Birth	No
M	24	24.1	Microphtalmia	Birth	OD: light, colors; OS: No
M*	51	26.6	Congenital cataracts and glaucoma	Birth	No
F	61	33.1	Retinopathy of prematurity	Birth	No
F	59	32.0	Unknown	Birth	Light
M	27	33.1	Bilateral retinoblastoma	2 years	No (2 eye prostheses)

F, female; M, male; y, years; OD, right eye; OS, left eye; *Rejected from the analysis.

2.2. Familiarization session

Intensity and (un)pleasantness of tastants were rated by indicating a number from 0 to 10 (intensity) or from -5 to 5 ((un)pleasantness), using the fingers of both hands. Prior to scanning, all participants were trained to use the intensity and pleasantness scales and familiarized with the rating procedure using the hands. Participants were also acquainted with the gustometer, consisting of a mouthpiece attached to syringes (60 mL) through separate tubing (1.7 m length; 3 mm diameter); all participants were allowed to explore the gustometer haptically or visually.

2.3. MRI data acquisition

Subjects were scanned using a 3-T Siemens Magnetom Trio MR scanner (Siemens, Erlangen, Germany) equipped with a 32-channel head coil (Invivo, FL, USA). All scanning sessions took place between 9 a.m. and 6 p.m. In order to limit possible side effects related to the ingestion of quinine, participants were instructed to eat a meal or a snack before the scanning session. Prior to the functional imaging runs, we acquired a T_1-weighted volume covering the head, using a magnetization prepared rapid gradient echo (MP-RAGE) sequence with the following parameters: repetition time (TR)/ echo time (TE) / inversion time (TI)/ flip angle (FA) of 2.3 s/ 2.98 ms/ 900 ms/ 9˚, 256x256 matrix, spatial resolution of 1x1x1 mm^3 voxels). Next, we collected single shot gradient echo-planar images (EPI) covering the whole-brain in an oblique orientation to the commissural plane (TR/TE of 2.95 s/ 30 ms, 90˚ flip angle, 64x64 matrix, field of view (FoV) of 192x192 mm, 45 slices with no gap, 3x3x3 mm^3 voxels). In each of the two functional runs, 340 dynamic images were acquired. Finally, we acquired a field map (FLASH, TR/TE short/TE long/FA 497 ms/4.92 ms/7.38 ms/60◦, 64x64 matrix with a resolution of 3x3x3 mm^3 voxels, 45 slices) to correct for static magnetic field inhomogeneities. We tried to restrict head motion by placing comfortable padding around participants' heads.

2.4. Stimuli and stimulation equipment

Four different tastants ("weak sweet": sucrose 0.05 M; "strong sweet": sucrose 0.15 M; "weak bitter": quinine hydrochloride 0.04 mM; "strong bitter": quinine hydrochloride 0.08 mM) and artificial saliva (potassium chloride 1.25 mM + sodium bicarbonate 0.125 mM)

dissolved in distilled water were freshly prepared before the start of the fMRI sessions. During scanning, tastants and artificial saliva were manually delivered at a rate of 3 mL / 3 sec, using the gustometer. Prior to stimulus onset, an audio cue (Nordic Neuro Lab) warned the experimenter of the upcoming stimulus. This was followed by an auditory countdown to ensure a relatively constant flow of 3 mL / 3 s. A 3 mL volume of water was administered after each tastant for mouth rinsing. Participants were asked to swallow all liquids were during the scanning sessions.

2.5. Experimental fMRI procedure

Blindfolded participants underwent two fMRI runs, each with 30 stimulus presentations, resulting in a total of 60 stimulus presentations. In both runs, the four tastants were administered five times, whereas the artificial saliva was administered 10 times; tastants and artificial saliva were presented in a pseudo-randomized fashion. The 3-s lasting taste stimuli were separated by an inter-stimulus interval varying between 27 and 38 s (Fig. 1). An auditory warning cue indicated participants that stimulus delivery was imminent. The experimenter received another auditory cue about the nature of the tastant, followed by an auditory countdown ("3-2-1-stop") to help achieve a relatively constant flow of 3 mL/ 3 s. Then, a second auditory cue urged participants to rate the intensity (run 1) or pleasantness (run 2) of the stimulus by using the response keys. The average time between the end of stimulus delivery and the response cue was 7 s, with a jitter from 4 to 11 s. Participants had 5 s (jitter from 4 to 7 s) to answer; they had to keep the fluid in the mouth until they heard the swallow cue ("Swallow"). Immediately thereafter, 3 mL of water was administered to rinse the mouth (3 s), which was followed by a second "swallow" cue, signalling participants to swallow again. The total duration of each run was 1003 s; the run order (intensity versus pleasantness) was counterbalanced between subjects. Swallowing was temporally separated from the other events because it can elicit important head movements. To minimize artefacts due to head movements, the timing of the image frames corresponding to swallowing and rinsing were locked to the repetition time (TR) and subsequently modelled using "scan nulling regressors" (Lemieux *et al*., 2007).

One blind and one sighted participant choked during swallowing and had to abort one of their functional runs. Therefore, 9 blind and 13 sighted participants successfully completed the intensity run, whereas 8 blind and 14 sighted participants finished the pleasantness run.

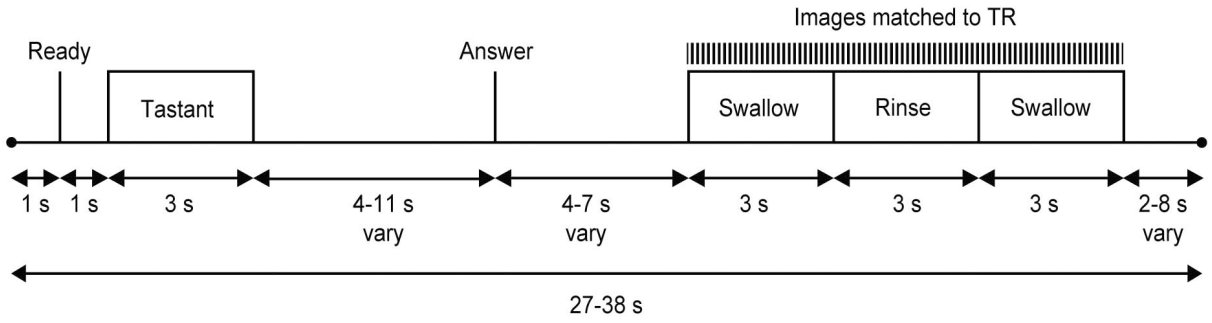

Fig. 1. Mixed event-related design illustrating stimulus presentation procedure. Blindfolded participants were asked to listen to task-related auditory cues. A "ready" ring tone warned participants of the taste delivery. After receiving the tastant, the subject was asked to keep the liquid in his mouth while he/she rated its intensity (run 1) or pleasantness (run 2). Then, another verbal cue indicated that participants had to swallow the tastant. This was followed by the instructions to rinse the mouth with distilled water and to swallow the rinsant. The MR images corresponding to swallow and rinse were matched to the image repetition times (TR) so that they could be modelled in the fMRI data analysis.

Prior and following the fMRI session, participants rated their hunger on a 5-point rating scale with 1 as "not hungry at all" and 5 as "extremely hungry". Hunger ratings were used as possible covariate in the ensuing data analyses (explained below).

2.6. Statistical analysis of the behavioural data

For each individual, we calculated the mean intensity and pleasantness ratings for the five taste conditions. To test for group differences, two 2-way (2 groups x 5 tastants) analyses of covariance (ANCOVAs) were carried out on the mean intensity and pleasantness ratings whereby age (De Graaf & Zandstra, 1999), gender (Sartor *et al*., 2011), BMI (Sartor *et al*., 2011) and hunger ratings (Laeng *et al*., 1993) were entered as possible covariates. The inclusion of these covariates was inspired by studies showing that the perceived intensity of sweetness positively varies with age (De Graaf & Zandstra, 1999), that younger subjects rate highly concentrated sucrose dilutions as more pleasant than older participants (De Graaf &

Zandstra, 1999), that females find sweet solutions less pleasant than males (Sartor *et al*., 2011; Laeng *et al*., 1993), and that obese subjects perceive sweet and salty as less intense than normal-weighted participants (Sartor *et al*., 2011). Finally, being hungry increases the perceived pleasantness of foods, creating an alliesthesia effect (Laeng *et al*., 1993).

As the hunger ratings were not normally distributed in each group (Shapiro-Wilk test), we used a Mann-Whitney U-test to assess potential group differences. Results were considered as statistically significant at $p < 0.05$, using a Bonferroni correction for multiple comparisons.

2.7. Processing and statistical analysis of fMRI data

We used SPM8 (statistical parametric mapping 8; www.fil.ion.ucl.ac.uk/spm/) for image processing and statistical analysis. In order to address the susceptibility-by-movement interaction, we used the FieldMap Toolbox of SPM8 and the reconstructed phase and magnitude images of the FLASH sequence described above. An unwrapped field map was calculated and then converted to a voxel displacement map (VDM) (Hutton *et al.*, 2002; Jezzard & Balaban, 1995) that was co-registered to the first EPI volume of each fMRI session. EPI time-series were corrected for slice-timing and realigned to adjust for movement following correction for spatial distortions caused by the gradient system. The resulting EPI images were spatially normalized to the MNI template, resampled to 3 mm isotropic voxels, and smoothed with an 8 mm full width at half maximum isotropic Gaussian kernel.

Statistical analysis was performed separately for each voxel using a general linear model formulation of SPM8. At the individual level (fixed effect), we defined separate regressors for the experimental condition of interest, i.e. tastes and saliva. The condition regressors were modeled by convolving a delta function after stimulus onset with the canonical hemodynamic response function (HRF); the rating responses were modeled by convolving delta functions (representing each button press) with the canonical HRF. A high-pass filter with a cut-off period of 128 s removed low frequency drifts in BOLD signal. Effect of motions during swallowing were modelled using "scan nulling regressors" (Lemieux *et al*., 2007) whereby 4 regressors, each in the form of a Heaviside function corresponding to a scan were included, spanning a 12-s interval (4 x TR) beginning with the first swallow scan to account for possible T1 and history effects.

The individual contrast images for the comparison of each type of tastant (TASTES > BASELINE, SALIVA > BASELINE) were entered into a random-effects analysis at the group level. The design matrix was configured as a multiple ANOVA with the factors group (blind, sighted) and tastants (TASTES, SALIVA). We controlled for the effects of age and gender because older adults activate their taste cortices more strongly than younger adults (Jacobson *et al*., 2010), and because men activate more strongly their insula compared to females when tasting bitter (Haase, *et al*., 2011). We thresholded the whole-brain *t*-value maps at $p \leq 0.005$, uncorrected, using a minimum cluster size of 10 contiguous voxels.

2.8. Post-hoc analysis

We tested whether the taste-induced BOLD signal changes within the hypothalamus correlate with the hunger ratings that were acquired prior the fMRI session in each group. The design matrix was configured as a multiple regression analysis whereby individual hunger ratings were entered as a covariate of interest interacting with the factor group and controlling for age and gender. We thresholded the whole-brain *t*-value maps at $p \leq 0.005$, uncorrected, using a minimum cluster size of 10 contiguous voxels.

3. Results

3.1. Subjective perception of tastants

Fig. 2 shows that intensity (A) and pleasantness (B) ratings of the tastants did not differ between blind and sighted participants. Only the hunger ratings following the fMRI session ($p = 0.021$) affected the perceived pleasantness of the tastants, whereas none of the covariates affected intensity ratings. The AN(C)OVAs revealed significant tastant effects (intensity $p = 0$; pleasantness $p = 0.002$), but no group effect (intensity $p = 0.319$; pleasantness $p = 0.357$) or group x tastant interaction (intensity $p = 0.469$; pleasantness $p = 0.074$). Post-hoc pairwise comparisons indicated that weak and strong sweet were rated differently for both intensity ($p = 0$) and pleasantness ($p = 0.007$). Similarly, weak and strong bitter were rated differently for both intensity ($p = 0$) and (un)pleasantness ($p = 0.002$). All tastants were judged as more intense compared to saliva ($p = 0$). The two sweet conditions were more pleasant than saliva ($p = 0$), whereas the two bitter conditions were less pleasant than saliva ($p < 0.008$).

The Mann-Whitney U-tests further revealed that hunger ratings, both before (U(1) = 57.0; p = 0.734) and after (U(1) = 56.0; p = 0.688) the fMRI session, did not differ across groups.

Fig. 2. Taste intensity (A) and pleasantness (B) ratings. Congenitally blind (CB) and sighted controls (SC) subjects did not differ in intensity and pleasantness ratings. In both groups, higher concentrations of the tastants were judged as more intense and more (un)pleasant compared to the low concentrations. Data are presented as the mean ± SEM. * p < 0.05; ** p < 0.01; *** p < 0.001.

3.2. Imaging results

The main effect of tasting was examined by a global conjunction analysis of the contrast (TASTES > SALIVA) in both groups. As illustrated in Fig. 3 and reported in Table 2, this analysis revealed that compared to artificial saliva, tastes evoked a stronger BOLD signal in the primary taste cortex, i.e. left ventral insula, and in an area extending from left post-central gyrus to the ipsilateral inferior parietal lobule.

We tested for purported group differences using the group x tastant interaction. As illustrated in Fig. 4 and reported in Table 2, blind individuals activated less strongly than their sighted counterparts (BLIND [TASTES > SALIVA] < SIGHTED [TASTES > SALIVA]) the

right posterior insula and overlying Rolandic operculum, together with bilateral cingulate cortex, left supramarginal gyrus and bilateral hypothalamus. Importantly, no brain regions were more strongly activated by the blind participants, including the occipital cortex, even after lowering the threshold to $p < 0.05$, k > 50 voxels (UNC).

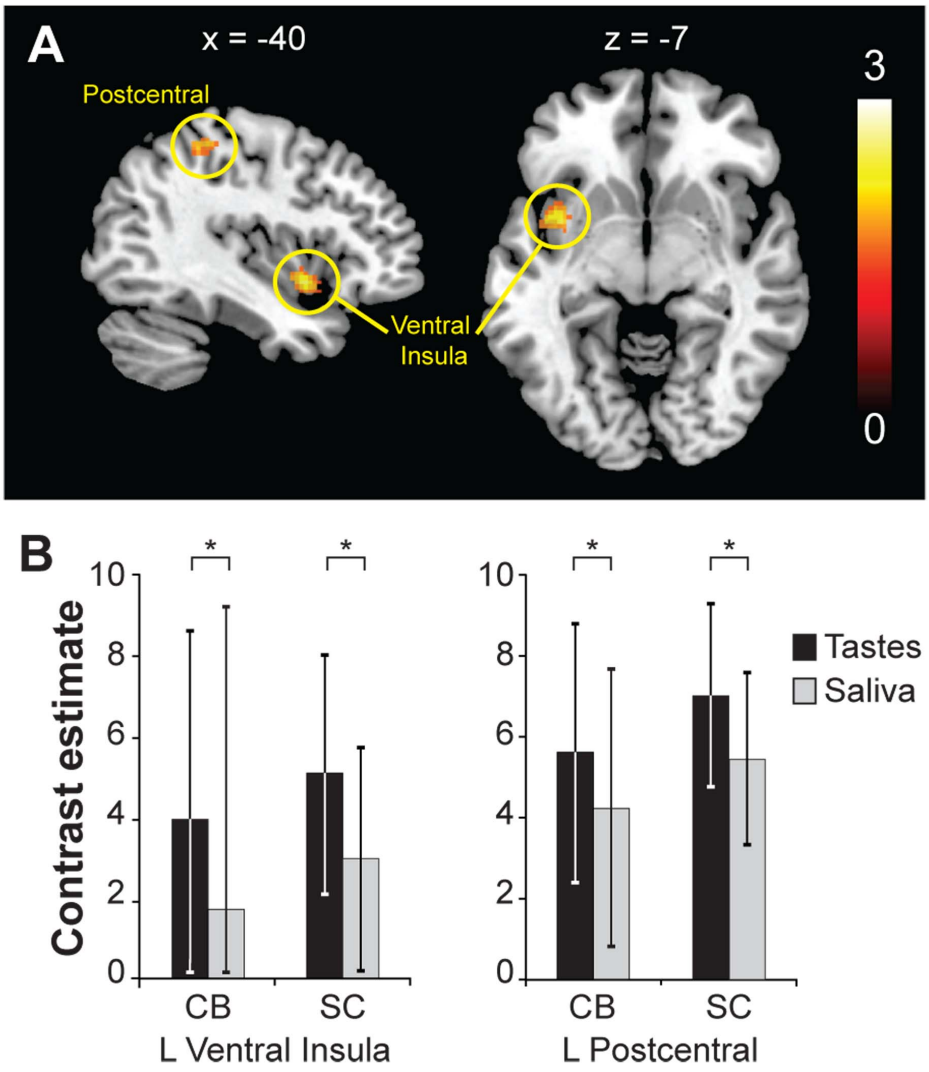

Fig. 3. Taste-induced BOLD signal increases. T-statistical map (**A**) and bar charts (**B**) showing areas and contrast estimates (± 90% confidence interval) where BOLD signal increases were significantly stronger for TASTES compared to SALIVA in both blind (CB) and blindfolded sighted (SC) subjects. The coordinates refer to the Montreal Neurological Institute (MNI) space. The threshold was set at $p = 0.005$, uncorrected, k > 10 voxels, and activation maps are displayed on the ch2better template provided by MRIcron. The right hemisphere corresponds to the right of the image. L, left.

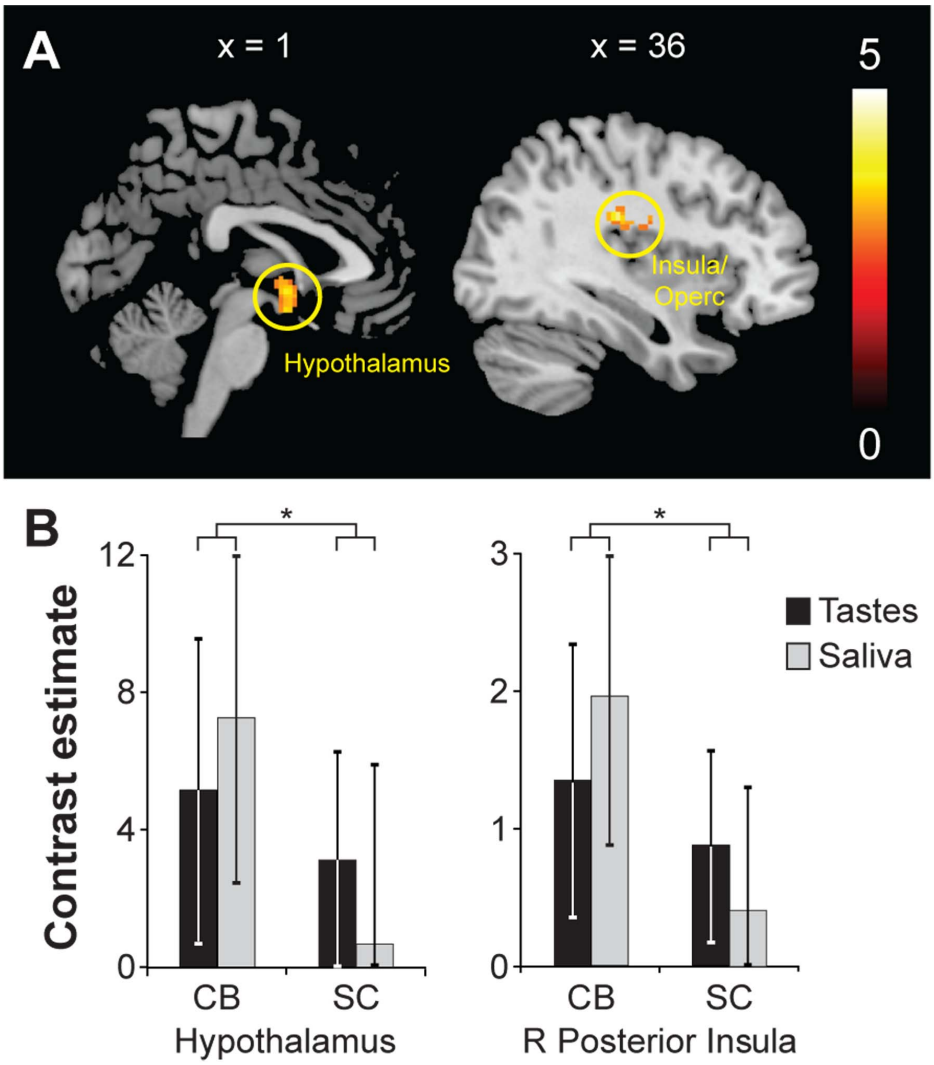

Fig. 4. **Areas with reduced taste-related responses in congenitally blind subjects.** T-statistical map (**A**) and bar charts (**B**) showing areas and contrast estimates (± 90% confidence interval) where BOLD signal increases were lower in blind (CB) compared to blindfolded sighted (SC) subjects when tasting (TASTES > SALIVA). Convention as in Fig. 3. R, right; Operc, Rolandic operculum.

3.3. Post-hoc imaging results

The group difference in hypothalamic activity was unexpected. As this region is modulated by feelings of hunger (Burton *et al*., 1976), we did a post-hoc regression analysis to explore a possible correlation between the taste-induced BOLD signal change within this region and pre-scan hunger ratings. Based on our earlier finding that blind individuals rely more strongly on their feeling of hunger (Gagnon et al., 2013; 2014a, b), we hypothesized a

stronger correlation between hypothalamic activity and hunger ratings in the blind. Fig. 5 shows that this was indeed the case. The activity within the hypothalamus correlated positively with the hunger ratings in the blind ($R_S = 0.634$; $p = 0.033$) but not in the sighted group ($R_S = 0.098$; $p = 0.370$). A cluster of 76 voxels was found at [0, -4, -12] with a peak T value of 4.16. This indicates that the more hungry blind participants were before scanning, the more strongly they activated their hypothalamus when tasting.

Table 2. Group similarities and differences when tasting (TASTES > SALIVA).

Brain Region		BA	MNI coordinates			cluster size	peak T
			x	y	z		
Conjunction							
Ventral Insula	L	13	-40	8	-8	139	2.54
Postcentral	L	2	-40	-36	54	95	2.05
Inferior Parietal	L	40	-36	-44	52	95	2.08
CB < SC							
Posterior Insula	R	13	32	-8	24	50	4.04
Rolandic Operculum	R	13	44	-16	22	124	3.00
Cingulate	R	24	18	-10	38	18	3.24
	L	24	-22	-18	38	37	3.89
Supramarginal	L	40	-46	-44	30	26	3.43
Hypothalamus	R		2	-2	-6	135	3.65

Peak T reflects the probability of the peak voxel of the cluster, uncorrected. The cluster size is expressed in voxels. MNI, Montreal Neurological Institute; R, right; L, left; BA, Brodmann area; CB, Congenitally blind; SC, Sighted control.

4. Discussion

The present brain imaging data confirm our hypotheses that taste-induced responses in the primary taste cortex (right posterior insula and overlying Rolandic operculum) and hypothalamus are weaker in blind compared to sighted controls, and that blind subjects do not recruit their occipital cortex during tasting. Our behavioral data confirm earlier findings that intensity and pleasantness ratings of tastants do not differ between blind and sighted subjects (Smith et al., 1993).

4.1. Insula/operculum

In line with results of previous brain imaging studies, tasting sweet and bitter activated the primary taste cortex in both groups (Small *et al*., 2003; De Araujo & Rolls, 2004). More specifically, we observed a large activation cluster in the left ventral insula, a region involved in processing sweetness (De Araujo & Rolls, 2004) and bitterness (Small *et al*., 2003). The same region is also involved in the processing of interoceptive signals (Critchley *et al*., 2004; Pattinson *et al*., 2009), pain (Raij *et al*., 2005) and trustworthiness (Winston *et al*., 2002).

The group comparison revealed that the right posterior insula and overlying Rolandic operculum were less strongly activated in blind compared to controls subjects. This region is involved in the recognition and intensity coding of tastants (Pritchard *et al*., 1999; Small *et al*., 2003; Grabenhorst & Rolls, 2008). However, the observed group difference cannot be attributed to subjective differences in intensity ratings since we did not find group differences in taste intensity ratings. It is possible that the reduced activity in primary taste cortex in the blind is related to their lower performance at identifying tastes, as we previously reported in a different cohort (Gagnon *et al*., 2013). Alternatively, our results could be explained by a reduced tastant exposure in congenital blindness resulting from a less diversified diet (Bilyk *et al*., 2009). A less diversified diet does not mean that blind subjects experience less often the five taste sensations; it rather implies a reduced exposure to a variety of tasty chemical molecules producing different neuronal, post-ingestive and physiological effects (e.g. Frank et al., 2008). This interpretation is concordant with results of studies showing that sensory learning and expertize are associated with enhanced activity in primary and/or higher order sensory cortices (Castriota-Scanderberg *et al*., 2005; Li *et al*., 2006; Elmer *et al*., 2012). Our results may therefore offer a neuronal underpinning for reduced gustatory sensitivity of congenitally blind individuals.

4.2. Hypothalamus

Congenitally blind individuals activated their hypothalamus less strongly than control subjects during tasting. The hypothalamus is the feeding center of the brain (Kroemer *et al*., 2012; Hillebrand, *et al*., 2002) that drives food intake by integrating metabolic needs and information about available foods (review in Garcia-Garcia *et al*., 2013); it is also involved in the representation of the expected subjective value of foods (Levy & Glimcher, 2011). In the

monkey, hypothalamic neurons fire to both the sight and the taste of foods (Burton *et al*., 1976). In humans, the region is more activated by anticipation of taste than by actual tasting (O'Doherty *et al*., 2002) and its activity correlates with levels of the orexigenic hormone ghrelin (Kroemer *et al*., 2012). Viewing pictures of food increases ghrelin levels (Schussler *et al*., 2012) and intravenous injection of ghrelin not only increases appetite but also induces visual mental imagery of favourite foods (Schmid *et al*., 2005).

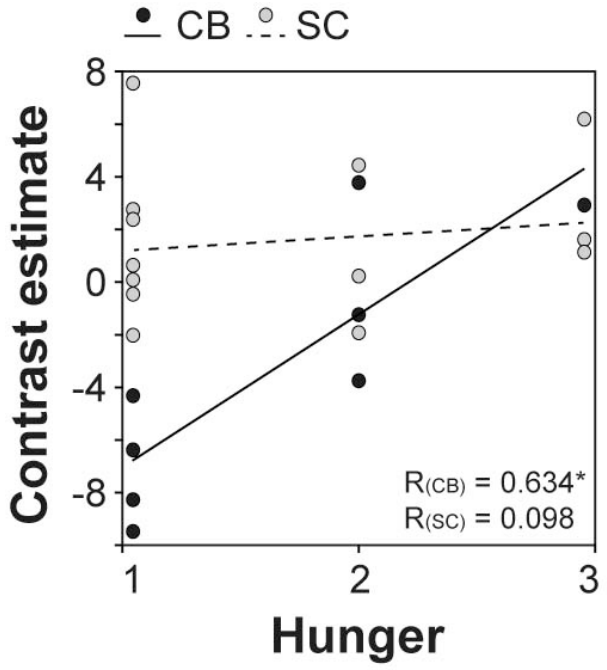

Fig. 5. Correlation between hunger ratings and hypothalamic activity. Blind but not sighted control subjects showed a positive correlation between hunger ratings prior the fMRI session and BOLD signal amplitude in the hypothalamus (TASTES > SALIVA). Black circles and plain line, congenitally blind (CB); Grey circles and dotted line, sighted controls (SC); R, Correlation coefficient. *Considered significant at $p < 0.05$.

Although there were no group differences in hunger ratings, the taste-induced BOLD signal increase in the hypothalamus correlated positively with the hunger ratings in the blind group only. Since the detection of foods or drinks in the exterior environment is far more difficult in the absence of vision, it is possible that the integration of food availability with metabolic needs takes place during tasting in blind individuals, whereas this happens primarily through vision in the sighted. The hypothalamic response in the blind could reflect the desired

value of the tastant following homeostatic evaluation mainly through interoceptive (taste and hunger) cues. More studies are needed to better understand the impact of visual impairment on food-related hypothalamic functions. This is important considering the beneficial role that feeding may have in entraining circadian rhythms that are often disturbed in blind individuals (Mistlberger & Skene, 2005; Yannielli *et al*., 2007).

4.3. Occipital cortex

This is the first study showing that the occipital cortex of congenitally blind subjects is not recruited during an active sensory task. Gustation therefore distinguishes itself from olfaction (Kupers *et al*., 2011), touch (Amedi *et al*., 2010; Matteau *et al*., 2010; Ptito *et al*., 2012) and audition (Gougoux *et al*., 2009; Lewis *et al*., 2011) that all recruit the occipital cortex in congenitally blind individuals. Studies using sensory-substitution devices have further demonstrated that this occipital recruitment is training-dependant (Ptito *et al*., 2005; Kupers *et al*., 2006; Striem-Amit *et al*., 2012). We therefore explain the absence of crossmodal plasticity by the blind's reduced gustatory training due to various blindness-related obstacles related to food access and consumption (Bilyk *et al*., 2009). Alternatively, the absence of overlap in the perceptual reach of vision and taste, involved in perceiving the external and internal worlds, respectively (review in Gagnon *et al*., 2014a) prevents the use of the sense of taste to compensate for the absence of vision.

Interestingly, the absence of crossmodal plasticity during taste processing in congenital blindness is reminiscent to that observed in congenital anosmic subjects who activate their medial orbitofrontal cortex less strongly by taste stimuli, compared to normal smelling individuals (Gagnon *et al*., 2014b). Our data add evidence to the multimodality of taste perception by showing that vision, like smell (Gagnon *et al*., 2014b), is essential to taste processing and that no compensatory crossmodal activation of the occipital cortex occurs during tasting in congenitally blind individuals.

5. Conclusion

Our brain imaging results indicate that congenitally blind subjects process taste information differently from sighted controls. The weaker activations observed in right posterior insula, overlying Rolandic operculum and bilateral hypothalamus combined with the

absence of occipital activation may provide a neurological underpinning for their reduced taste perception. Moreover, our data indicate that gustation distinguishes itself from audition, touch and olfaction by not triggering compensatory crossmodal responses in the occipital cortex.

Author contributions

Conceived and designed the experiments: LG, RK, MP. Performed the experiment and analyzed the data: LG. Wrote the paper: LG, RK, MP.

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Article 4

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Neural correlates of taste perception in congenital olfactory impairment

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Abstract

Olfaction and gustation contribute both to the appreciation of food flavours. Although acquired loss of smell has profound consequences on the pleasure of eating, food habits and body weight, less is known about the impact of congenital olfactory impairment on gustatory processing. Here we examined taste identification accuracy and its neural correlates using functional magnetic resonance imaging (fMRI) in 12 congenitally olfactory impaired individuals and 8 normosmic controls. Results showed that taste identification was worse in congenitally olfactory impaired compared to control subjects. The fMRI results demonstrated that olfactory impaired individuals had reduced activation in medial orbitofrontal cortex (mOFC) relative to normosmic subjects while tasting. In addition, olfactory performance as measured with the Sniffin' Sticks correlated positively with taste-induced blood-oxygen-level dependent (BOLD) signal increases in bilateral mOFC and anterior insula. Our data provide a neurological underpinning for the reduced taste perception in congenitally olfactory impaired individuals.

Keywords: taste; smell; congenital olfactory impairment; fMRI; orbitofrontal cortex.

1. Introduction

Our appreciation of fine foods or drinks largely comes from a rich diversity of flavours perceived mainly by our sense of smell, together with taste (e.g. sweet, salty) and trigeminal (e.g. temperature, texture) sensations (Auvray & Spence, 2008; Lundstrom, Boesveldt, & Albrecht, 2011). The loss of olfaction has therefore strong repercussions on flavour perception but it remains unclear how this is manifested at the cerebral level. Studies have demonstrated that the olfactory and gustatory systems largely overlap. Following activation of taste receptors, taste information travels from the VII, IX and X cranial nerves to reach first the nucleus of the solitary tract of the brainstem, followed by the ventral posterior medial nucleus of the thalamus and then converges towards the primary and secondary taste cortices in the insula/operculum and orbitofrontal cortex (OFC), respectively (Sewards, 2004). Smell information, on the other hand, is conveyed by the olfactory nerve (I) and synapses first in the olfactory bulb before reaching the piriform and entorhinal cortices (primary olfactory cortices), followed by various higher order olfactory areas such as the amygdala, cingulate cortex, insula and orbitofrontal cortex. According to the traditional view, taste-odour integration occurs in the orbitofrontal cortex (Rolls, 2001; 2008; De Araujo, Rolls, Kringelbach, McGlone, & Phillips, 2003) and insula (Small & Prescott, 2005; Verhagen & Engelen, 2006). However, recent evidence from rodent studies challenges the classical view (Small, Veldhuizen, & Green, 2013) as taste neurons were also recorded within the posterior piriform cortex (Maier, Wachowiak, & Katz, 2012). This close anatomical relationship between the olfactory and gustatory systems suggests that odour impairments may affect the central processing of taste.

Odour impairments are common and affect nearly 5% of the population (Karstensen & Tommerup, 2011). Acquired anosmia resulting from traumatic brain injury, infection of the upper respiratory tract or other diseases leads to a decreased appetite and lower interest in eating, changes in body weight, disturbances in affective behaviour (e.g. depression), and a reduced quality of life (Ferris *et al*., 1985; Mattes & Cowart, 1994; Van Toller, 1999; Miwa *et al*., 2001; Temmel *et al*., 2002; Aschenbrenner *et al*., 2008). In addition, these patients display decreases in gustatory (Gudziol, Rahneberg, & Burkert, 2007) and trigeminal (Gudziol, Schubert, & Hummel, 2001; Frasnelli, Schuster, & Hummel, 2010) sensitivity. At the cortical level, brain imaging studies on trigeminal processing using event-related potentials (Frasnelli

Schuster, & Hummel, 2007a) and functional magnetic resonance imaging (fMRI; Iannilli, Gerber, Frasnelli, & Hummel, 2007) in patients with acquired anosmia compared to controls revealed lower activity in chemosensory brain areas, such as the right somatosensory cortex and left insula (Iannilli *et al*., 2007).

In contrast to acquired anosmia, the consequences of congenital absence of smell on eating habits and flavour processing have received little attention. The few published studies failed to observe differences in eating patterns or electrogustatory and trigeminal sensitivity in individuals with isolated congenital anosmia (Frasnelli, Schuster, & Hummel, 2007b; Croy, Negoias, Novakova, Landis, & Hummel, 2012) or Kallmann syndrome (Hasan, Reddy, & Barsony, 2007). In sharp contrast, Levy and colleagues (2013) found that nearly half of their congenitally anosmic patients had lower taste detection and taste identification thresholds compared to normosmics, indicating that life-long olfactory deprivation can have a negative effect on taste function.

Here, we investigated taste perception in a cohort of otherwise healthy participants with isolated congenital olfactory impairment (COI). All participants had close relatives also affected with isolated COI, indicating a genetic pre-disposition of the disorder. Their symptoms could not be ascribed to Kallmann syndrome or other known genetic syndromes, in which olfactory impairment is part of a larger clinical picture with various other symptoms. COI patients are particularly interesting because of their life-long absence of odour perception that may have changed the maturation of brain pathways and triggered crossmodal neuroplastic rearrangements. The goal of the present fMRI study was to test whether COI tasting impairments are related to altered BOLD responses in gustatory- and olfactory-processing brain areas. Our main region of interest (ROI) was the medial orbitofrontral cortex (mOFC), as this region is the classical area where taste and smell information are combined into a flavour percept (De Araujo *et al*., 2003). The anterior insula and the piriform cortices (Small & Prescott, 2005; Maier, *et al*., 2012; Small *et al*., 2013) were considered as secondary ROIs.

2.Methods

2.1.Participants

Twenty-five right-handed (Edinburgh handedness inventory; Oldfield, 1971) subjects participated in the fMRI experiment. Within the affected group of individuals (COI), 3 were from a Danish family and the remaining were Faroese and mixed Danish and Faroese origin. Gender and age-matched normosmic control subjects were recruited from the Faroese family cohort and from the Faroese community living in the Copenhagen area through advertising.

Table 1a. Demographic data of the participants.

Sex	Age (y)	TDI score	T sub-score	D sub-score	I sub-score	Family	Origins
Congenitally olfactory impaired							
M	56	7.3	1.3	3	3	a	Faroese
M	63	10.0	1.0	6	3	b	Faroese
F	24	10.3	1.3	6	3	v	Danish
M	50	10.3	1.3	4	5	f	Faroese
M	22	11.3	7.3	3	1	v	Danish
M*	54	12.3	1.3	5	6	b	Faroese
F	48	13.0	1.0	7	5	a	Faroese
F	62	13.0	1.0	6	6	a	Faroese
F	42	14.8	3.8	8	3	g	Faroese
F	29	16.3	1.3	6	9	a	Faroese
M	40	16.5	3.5	6	7	b	Faroese
F*	21	17.8	1.8	8	8	d	Faroese & Danish
F	47	21.0	5.0	9	7	b	Faroese
M	45	22.5	4.5	11	7	b	Faroese
Normosmic control							
F	55	30.5	9.5	9	12	c	Faroese
M	32	31.5	6.5	13	12	x	Faroese
M	33	32.8	5.8	15	12	x	Faroese
F	24	33.5	9.5	12	12	d	Faroese & Danish
F	43	33.8	8.8	13	12	d	Faroese
F	25	34.3	8.3	14	12	x	Faroese
M	35	36.5	8.5	14	14	x	Faroese
M	53	39.5	10.5	16	13	x	Faroese & Danish

Y, years; TDI, threshold-discrimination-identification; M, male; F, female; *excluded from the fMRI analysis; f and g, case studies; v, danish family; x, non-familial control. Families a, b, c and d could be linked to a common ancestor.

All subjects with COI reported to have a life-long inability to smell. Subjects living in the Faroe Islands or Denmark were examined by an otolaryngologist at the National hospital of the Faroe Islands or at the Vejle hospital in Denmark. The examination procedure included laryngoscopy of the nose and throat, a clinical interview with questions related to their history of olfactory dysfunction, head trauma, employment and pubertal development. Two subjects were excluded based on either childhood head trauma or chronic nasal infection. For the remaining sample, no other associated neuropathies could be related to the loss of smell. Demographic data of the subjects are given in Table 1a.

A trained radiologist assessed the T_1-weighted, T_2-weighted and FLAIR images for pathologies in the brain, nasal cavity, sinuses or nasal mucosa. This inspection led to the removal of one COI participant. Another COI subject was also removed from the fMRI analysis because of technical scanning problems. One control participant that showed presbyosmia related to age (62 years old) was excluded from the analysis to avoid heterogeneity within the otherwise normosmic control group (NC; n = 8; 4 females).

The groups were matched in terms of age, sex, body mass index (BMI), education and cognitive function (MoCA©) (Table 1b). Experiments were performed at the Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital Hvidovre in Denmark. The research ethics committee of the Faroe Islands [200812] and the capital region of Denmark approved the study [H-A-2009-063, 28963] and all subjects gave informed and written consent prior examination.

2.2.Olfactory Assessment

Examination of olfactory ability was done at the Danish Research Center for Magnetic Resonance, at Hvidovre Hospital, Denmark. We used the Sniffin' Sticks threshold-discrimination-identification (TDI) score (Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997; Hummel, Kobal, Gudziol, & Mackay-Sim, 2007; Table 1a) and history of odour perception, head trauma as well as medical and psychiatric illness obtained from the semi-structured interviews to exclude psychopathology and classify the participants into congenitally olfactory impaired (COI; TDI < 30.3; Hummel *et al*., 2007) and normosmic control (NC; TDI > 30.3) groups. All participants were also tested for phenylthiocarbamide (PTC) sensitivity using taste strips (Fisher scientific).

Table 1b. Descriptive data and statistics.

Measures	Group	Mean	± SEM	Statistic values*
Age (y)	COI	44	4	t(1) = -1.11; *p* = 0.28
	NC	38	4	
Education (y)	COI	12	1	t(1) = 1.21; *p* = 0.24
	NC	14	1	
MoCA© score	COI	27.2	0.74	U(1) = 32.5; *p* = 0.24
	NC	28.5	0.71	
Body mass index (kg/m^2)	COI	25.8	1.22	U(1) = 35.0; *p* = 0.79
	NC	25.1	0.71	
PTC sensitivity (+/total)	COI	11/12	N/A	x2(1) = 1.05; *p* = 0.34
	NC	6/8	N/A	

*Considered significant at $p \leq 0.05$. SEM, standard error of the mean; Y, years; PTC, phenylthiocarbamide; +, PTC taster; COI, Congenitally olfactory impaired; NC, normosmic controls; N/A, not applicable; t, Student t; U, Mann-Whitney U; x2, chi-square.

2.3.MRI data acquisition

Subjects were scanned using a 3-T Siemens Magnetom Verio MR scanner (Siemens, Erlangen, Germany) equipped with a 32-channel head coil (Invivo, FL, USA).

We collected single shot gradient echo-planar images (EPI) covering the whole-brain with BOLD contrast in an oblique orientation to the commissural plane (TR/TE of 2,15 s/ 26 ms, 78˚ flip angle, 64x64 matrix, FoV of 192x192 mm, 42 slices with no gap, 3 mm thickness, 3x3x3 mm^3 voxels). In each of the two functional sessions, 197 dynamic scans were acquired. Head motion was restricted with comfortable padding around the participant's head.

2.4.Stimuli and stimulation equipment

Three different tastants: sweet (sucrose; 0.028 M), salty (sodium chloride; 0.16 M), bitter (quinine hydrochloride; 0.024 mM) and solvent (deionised water) were prepared for the fMRI sessions. During scanning, tastants were manually delivered at a rate of 3 mL / 3 s, using a homemade gustometer consisting of a mouthpiece attached to syringes (60 mL) through separate tubing (length of 1.7 m; diameter of 3 mm). A 3 mL volume of water was

administered after each tastant to rinse the subject's mouth. All liquids were swallowed during scanning.

2.5.Experimental fMRI procedure

Participants underwent two fMRI runs with 25 stimulus presentations per run, resulting in a total of 50 stimulus presentations. In both runs, every tastant (sweet, salty and bitter) was administered 5 times whereas the control condition (water, solvent) was repeated 10 times, all presented in a pseudo-randomized fashion. As illustrated in Figure 1, the 3-s stimuli were separated by an inter-stimulus interval varying between 16 and 23 s. A visual warning cue ("Ready") presented on a retro projection screen indicated that the delivery of the tastant was imminent. At the same time, the experimenter received an auditory cue (MR Confon system) that informed him of the nature of the tastant. During stimulus delivery, he heard a count-down ("3-2-1-stop") and manually pushed the plunger of a syringe at a relatively constant flow of 3 mL / 3 s. Following tastant delivery, a second visual cue ("Answer") required the participant to indicate, in a forced-choice paradigm, the nature of the stimulus ("Sweet, Salty, Bitter, Water"; projected on the default screen display) using a computer-mouse key. The average time between the end of stimulus delivery and the response cue was 3 s, with a jitter from 0 to 6 s. Participants were asked to keep the fluid in their mouth until the swallow cue ("Swallow", appeared 3 s). Immediately after, 3 mL of water was administered to rinse the mouth ("Water", appeared 3 s), which was followed by the second "Swallow" cue signalling participants to swallow again. The mean total duration of each run was 488 s. Participants were instructed to swallow only when the swallow cue appeared, as swallowing can elicit important head movement. Respiratory motion was recorded throughout scanning with a respiration belt sampled at 50 Hz.

Following the fMRI session, participants were asked to recall the 3 tastants and rate their intensity and pleasantness on a 5-point rating scale with "1" as not perceptible or not pleasant and "5" as very strong or very pleasant.

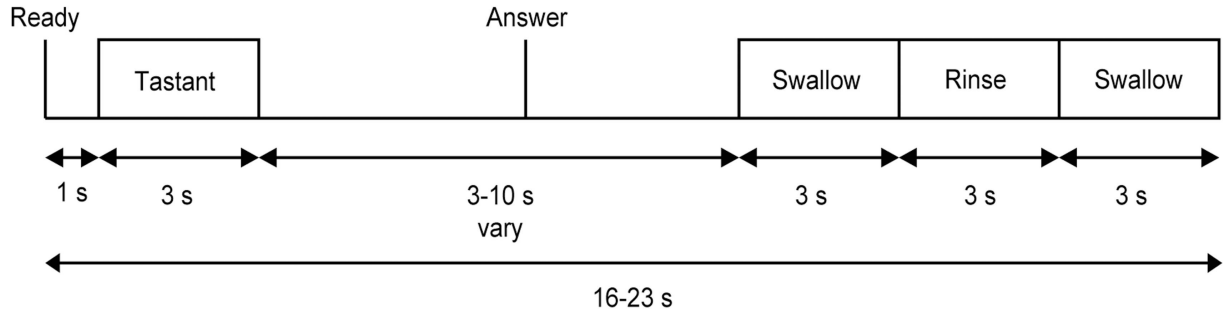

Fig. 1. Mixed event-related design illustrating one stimulus presentation. Participants were asked to fixate a cross and to follow the (Danish) written cues. A default screen identifies the nature of the four computer mouse keys (two for each hand) used to identify the sweet, salty, bitter or neutral tastes. The signal "Ready" warns the participant of the taste delivery. After receiving the tastant, the subject keeps the liquid in his mouth while he/she responds. Then, he/she swallows the liquid according to the instruction on the screen, rinses his mouth with deionised water and swallows a second time before the next trial.

2.6.Statistical analysis of the behavioural data

Based on the subjects' responses from the taste identification task, we calculated the number of hits, misses, false alarms and correct rejections. These measures were combined to estimate the sensitivity index d-prime following the signal detection theory method (Swets, 1961). A high d-prime indicates a good identification accuracy and a readily detected signal compared to noise. All variables were first assessed for normality using the Shapiro-Wilk test. To test for group differences in taste perception, we conducted 3 ANCOVAs with group (COI and NC) as independent variable, and the 3 tastes d-primes as dependant variables. Age, gender, PTC sensitivity and BMI were entered as possible covariates as taste sensitivity declines with age whereas women are better at tasting than men (Heft & Robinson, 2010). PTC tasters have lower sweetness and bitterness thresholds than PTC non-tasters (Hong *et al*., 2005) and a high BMI reduces the ability to identify tastants (Overberg, Hummel, Krude, & Wiegand, 2014). The subjective perception of tastants was analysed with 2 Student *t*-tests for independent samples.

2.7.Processing and statistical analysis of MRI data

To carry out the correlation analysis between the grey matter volume inside the ROIs and taste identification accuracy, we used voxel-based morphometry (VBM) data from a study

performed on the same subjects in our laboratory. A detailed description of the ROI and VBM analysis is provided in the Supplementary methods section.

2.8.Processing and statistical analysis of fMRI data

Image processing and statistical analysis were performed using SPM8 (statistical parametric mapping 8; www.fil.ion.ucl.ac.uk/spm/). EPI time-series were corrected for slice-timing and realigned to adjust for movement following correction for spatial distortions caused by the gradient system. The resulting EPI images were spatially normalized to the study specific template using diffeomorphic anatomical registration through exponential lie algebra (DARTEL), resampled to 2 mm isotropic voxels, and smoothed with an 8 mm full width at half-maximum isotropic Gaussian kernel.

Statistical analysis was performed separately for each voxel using a general linear model. At the individual level (fixed effect), we defined separate regressors for the experimental condition of interest, i.e. sweet, salty, bitter and solvent. The condition regressors were modeled by convolving a 3-s boxcar function after stimulus onset with the canonical hemodynamic response function (HRF); the responses were modeled by convolving delta functions (representing each button press) with the canonical HRF. A high-pass filter with a cut-off period of 128 s removed low frequency drifts in BOLD signal. The individual contrast images for the comparison of each TASTE vs. SOLVENT were then entered into a random-effects analysis at the group level. We used 2 different model designs to test our hypothesis. In the first model, the design matrix was configured as a multiple regression analysis entering the olfactory (TDI score as well as T, D or I sub-scores) or the gustatory (d-prime) measure as the covariate of interest controlling for age and gender (Jacobson, Green, & Murphy, 2010; Haase, Green, & Murphy, 2011). In the second model, the design matrix was configured as a 2-sample *t*-test with the COI and NC groups with age and gender entered as covariates of no interest. The whole-brain *t*-value maps were thresholded at $p \leq 0.001$ uncorrected and significance was assessed at the cluster level applying a statistical threshold of $p \leq 0.05$ and family-wise error (FWE) correction to control for multiple comparisons as implemented in SPM8. For the pre-defined ROIs, FWE correction only considered the voxels within the ROIs, applying the same statistical criteria for defining statistical significance.

3.Results

3.1.Identification and subjective perception of tastants

Figure 2 illustrates the behavioural data collected during (Figure 2a) and after (Figure 2b) the scanning sessions. Since none of the covariates varied significantly with the dependant variables, we used independent samples Student *t*-tests and Mann-Whitney U-tests to test for group differences (Table 2), depending on whether the data were parametric or not. We did not find group differences in subjective hedonic and intensity ratings of tastants. However, bitterness identification accuracy during scanning was worse in COI compared to NC subjects. Similarly, there was a trend towards a worse identification accuracy for saltiness in COI compared to NC subjects. Lastly, sweetness identification accuracy was similar for both groups.

Table 2. Behavioural data and statistics.

Measures		Group	Mean	± SEM	Statistic values*
Taste identification d-prime					
Sweet		COI	2.43	0.31	$t(1) = 1.26$, $p = 0.23$
		NC	3.00	0.30	
Salty		COI	2.95	0.31	$U(1) = 29.5$, $p = 0.16$
		NC	3.59	0.16	
Bitter		COI	2.41	0.18	$t(1) = 2.14$, $p = 0.05$*
		NC	3.06	0.25	
Subjective ratings					
Sweet	Hedonic	COI	3.00	0.41	$t(1) = 1.52$, $p = 0.15$
		NC	3.75	0.25	
	Intensity	COI	2.56	0.24	$U(1) = 32.0$, $p = 0.74$
		NC	2.75	0.31	
Salty	Hedonic	COI	1.67	0.29	$U(1) = 31.5$, $p = 0.67$
		NC	1.88	0.35	
	Intensity	COI	4.00	0.37	$U(1) = 31.5$, $p = 0.67$
		NC	4.25	0.37	
Bitter	Hedonic	COI	1.11	0.11	$U(1) = 21.0$, $p = 0.17$
		NC	1.88	0.40	
	Intensity	COI	3.88	0.35	$U(1) = 21.5$, $p = 0.17$
		NC	4.56	0.20	

*Considered significant at $p \leq 0.05$. SEM, standard error of the mean; COI, congenitally olfactory impaired; NC, normosmic control; t, Student t; U, Mann-Whitney U.

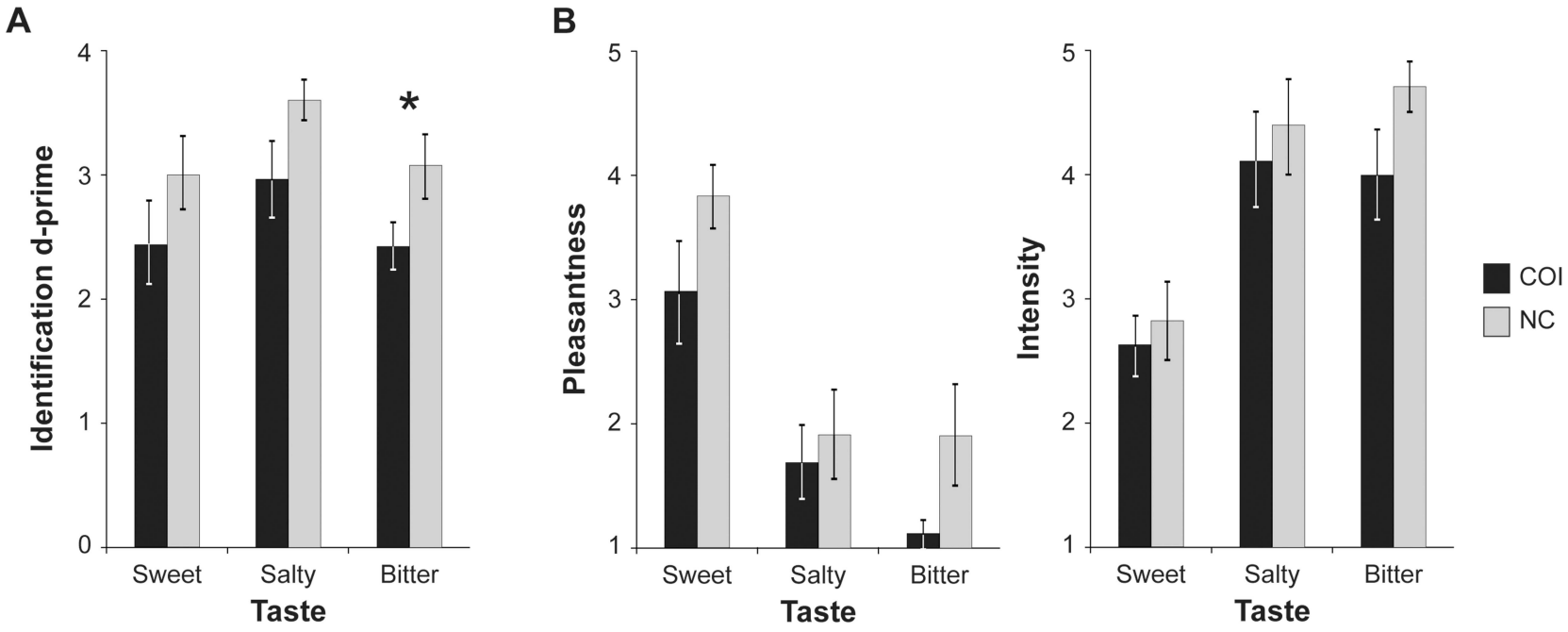

Fig. 2. Bar charts showing the mean ± standard error of the mean (SEM) for taste identification accuracy (**A**) and subjective perception of tastants (**B**) in congenitally olfactory impaired (COI) and normosmic control (NC) subjects. The asterisk shows significant results at $p \leq 0.05$. COI have significantly worse bitter identification accuracy than NC subjects but similar identification accuracy for sweet and salty. The groups did not differ for taste hedonic and intensity ratings.

3.2.Imaging results

Based on our behavioural results, we focused our fMRI analysis on the brain activity for bitterness, the tastant that COI subjects had the most difficulty to identify. Post-hoc analyses for sweet and salty are presented in the Supplementary materials section.

Figure 3 illustrates the lower BOLD response in COI compared to NC subjects in bitterness-induced brain responses. The ROI analysis revealed that only the left mOFC was significantly less activated in COI compared to NC subjects when tasting bitterness ($p_{FWE\text{-}cluster}$ = 0.04).

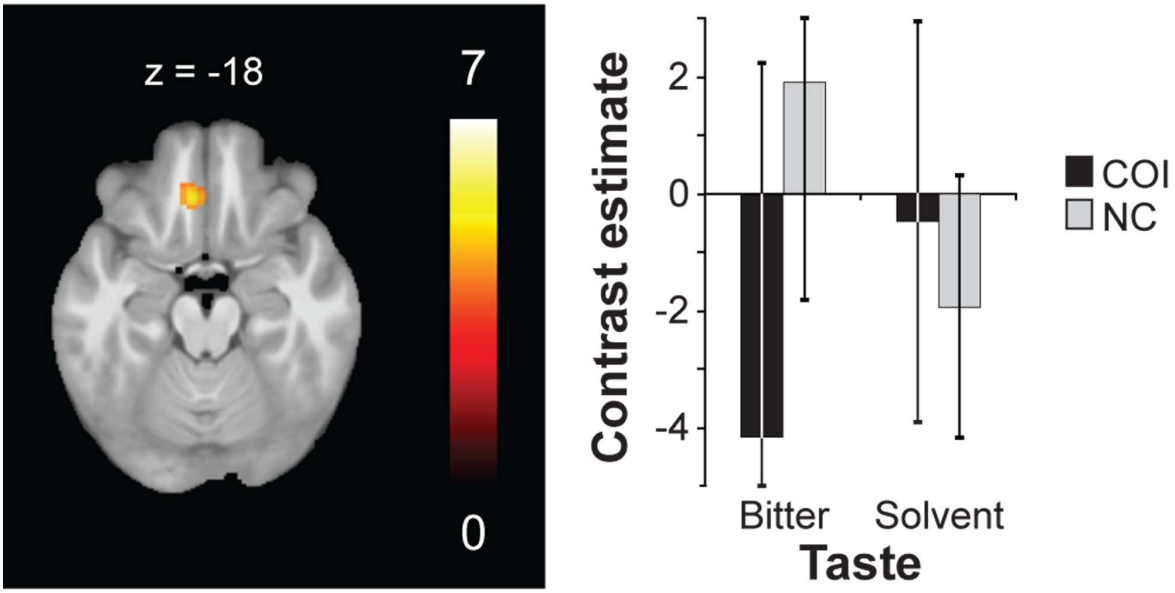

Fig. 3. T-statistical map and bar chart showing areas and contrast estimates (± 90% confidence interval) where BOLD signal increases are significantly lower in congenitally olfactory impaired (COI) compared to normosmic controls (NC) when tasting bitterness. The coordinate over the slice refers to the Montreal Neurological Institute (MNI) space. The threshold is set at p = 0.001, uncorrected, and activation maps are displayed on the group template. The right hemisphere corresponds to the right of the image.

Figure 4 shows the positive correlations between the threshold (T) sub-score (Figure 4a) and total TDI score (Figure 4b) and BOLD signal changes for bitterness. The whole brain analysis reveals 3 significant clusters in the left frontal lobe that varied with the olfactory threshold, namely in the medial orbitofrontal cortex, medial superior frontal gyrus and pars triangularis of the inferior frontal gyrus (Table 3). None of the other olfactory measures significantly co-varied with changes in BOLD signal for bitterness. In line with this, our ROI

analysis further revealed that the T sub-score, but not the discrimination (D) and identification (I) sub-scores, varied statistically with BOLD signal changes for bitterness. More specifically, BOLD signal changes correlated positively with the olfactory threshold in mOFC (Figure 4a; $p_{FWE\text{-}cluster} = 0.01$) and anterior insula (Figure 4a; $p_{FWE\text{-}cluster} = 0.04$). When using the total TDI score, there was a significant linear relationship with the regional BOLD response in the mOFC (Figure 4b; $p_{FWE\text{-}cluster} = 0.05$). Finally, both the whole-brain and the ROI analysis reveal that the ability to identify bitterness did not vary significantly with the BOLD signal while tasting.

Figure 5 illustrates the strong positive correlation between mOFC grey matter volume (as measured by VBM) and bitterness identification. Whole brain analysis revealed two significant clusters in bilateral rectus gyri. In line with this, the ROI analysis further confirmed that the bilateral mOFC was the only area showing a significant correlation between bitter identification and grey matter volume (figure 5). A summary of all the whole-brain and ROI analysis is provided in Tables 3 and 4, respectively.

Table 3. Summary of the whole-brain analysis.

Brain Region		BA	MNI coordinates			cluster	peak	peak
			x	y	z	size	*p*	T
fMRI								
Positive correlation with T-score								
Medial orbitofrontal	L	11	-6	32	-18	393	0.01	6.78
Medial superior frontal gyrus	L	10	-6	64	4	691	0.00	6.28
Inferior frontal gyrus	L	45	-50	22	6	594	0.00	5.53
VBM								
Positive correlation with bitter d-prime								
Rectus gyrus	R	11	10	39	-22	991	0.05	4.97
	L	11	-6	24	-27	1066	0.03	7.34

Peak *p* reflects the probability of the cluster using the FWE correction for multiple tests. The cluster size is expressed in voxels. MNI, Montreal Neurological Institute; R, right; L, left; BA, Brodman area.

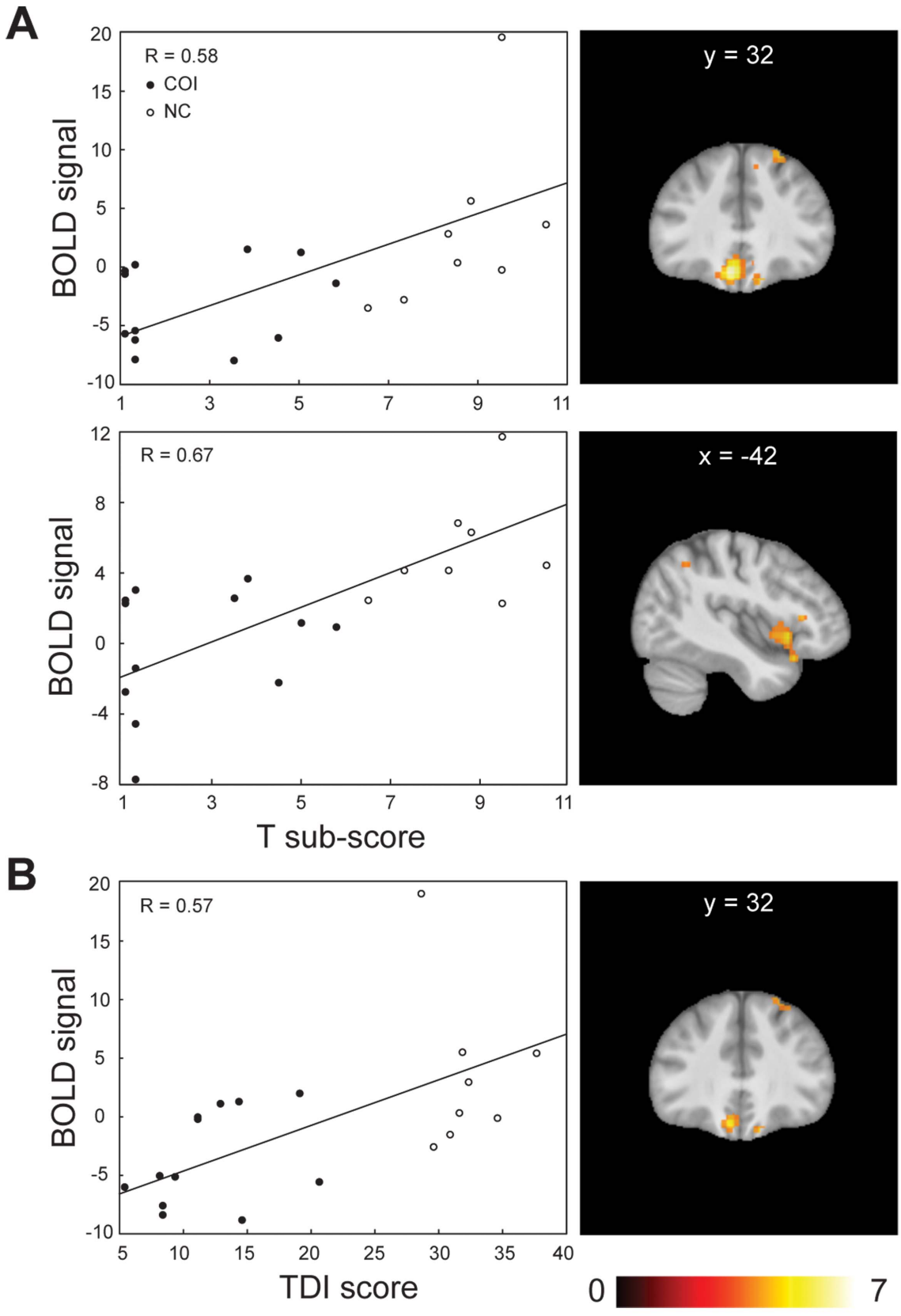
A
R = 0.58
COI
NC
BOLD signal
y = 32
R = 0.67
BOLD signal
x = -42
T sub-score
B
R = 0.57
BOLD signal
y = 32
TDI score
0
7

Fig. 4. Scatter plots and T-statistical maps showing areas where BOLD signal increases when tasting bitterness strongly correlate with the ability to smell. A: The olfactory detection threshold (T sub-score) varies positively with the BOLD signal (mean eigenvalues) in bilateral mOFC and anterior insula. B: The total Sniffin' Sticks TDI score varies positively with the BOLD signal in bilateral mOFC. The coordinates over the slices refer to the Montreal Neurological Institute (MNI) space. The visualization threshold is set at p = 0.001, uncorrected, and activation maps are displayed on the group template. The right hemisphere corresponds to the right of the image. Filled circles, congenitally olfactory impaired (COI); Open circles, normosmic controls (NC). T, threshold; TDI, threshold-discrimination-identification; R, Pearson correlation coefficient.

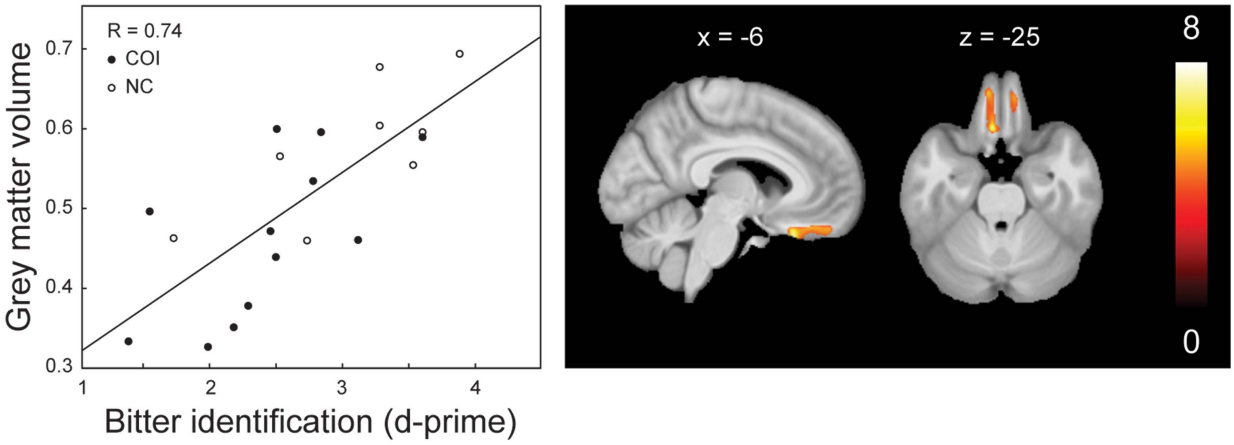

Fig. 5. Scatter plot and T-statistical map showing areas where VBM values correlate with bitter identification accuracy. The bitter identification d-prime varies positively with the volume of grey matter within bilateral mOFC. The coordinate over the slice refers to the Montreal Neurological Institute (MNI) space. The visualization threshold is set at p = 0.001, uncorrected, and VBM map is displayed on the group template. The right hemisphere corresponds to the right of the image. Filled circles, congenitally olfactory impaired (COI); Open circles, normosmic controls (NC). R, Pearson correlation coefficient.

4.Discussion

Compared to normosmic controls, congenitally olfactory impaired subjects exhibit bitterness identification impairment combined with a reduced activation of the deprived higher-order olfactory cortices. Moreover, the grey matter volume within the mOFC correlates

positively with bitterness identification accuracy, demonstrating a functional and structural underpinning of this taste impairment.

Our results are consistent with previous studies showing similar taste deficits in isolated congenitally (Levy, Degnan, Sethi, & Henkin, 2013) and acquired (Gudziol *et al*., 2007; Landis *et al*., 2010) anosmic patients. Among the three tastants used in our experiment, bitterness was the most difficult to identify by olfactory impaired subjects. This is in accordance with Gudziol's study (2007) where bitterness was also the most difficult taste to identify by acquired anosmic subjects, followed by salty and acid. Interestingly, the bitterness impairment in COI subjects was not related to PTC sensitivity, as a similar number of PTC tasters and non-tasters were present in both populations. Bitterness is traditionally considered as the taste signalling the potential presence of poisonous substances, such as alkaloids, and therefore threat and danger (Hladik, Pasquet, & Simmen, 2002). This view is interesting as anosmic subjects are also impaired in recognising various environmental hazards involving foods. For example, they "scorch food" and eat "spoiled foods" more often than normosmic subjects (Croy *et al*., 2012). The failure to identify bitterness might increase the ingestion of scorched food and/or unfamiliar poisonous foods (such as exotic berries) and, in this way, contribute to increase the frequency of food accidents.

The fMRI data further revealed that COI subjects less strongly recruit their mOFC compared to NC when tasting bitterness. Interestingly, we also found a positive correlation between odour performance and BOLD signal changes for bitterness in regions that integrate taste and smell information, namely the mOFC and anterior insula. Taken together, our data indicate that olfaction might have an influence on taste perception since congenital olfactory impairment leads to a lower signal in flavour processing brain areas during tasting.

4.1.Medial orbitofrontal cortex

The lower BOLD signal observed in the mOFC of our COI participants is in accordance with structural and metabolic changes within this region following the loss of smell perception. These changes include grey matter volume reductions (Bitter, Bruderle, *et al.*, 2010; Bitter, Gudziol, *et al*., 2010), increased grey matter thickness (Frasnelli, Fark, Lehman, Gerber, & Hummel, 2013), hypometabolism (Varney, Pinkston, & Wu, 2001) and hypoperfusion (Eftekhari *et al*., 2006; Atighechi *et al*., 2009). Two previous studies reported a

positive correlation between olfactory performance and grey matter thickness in the mOFC in healthy individuals (Frasnelli *et al.*, 2010; Seubert, Freiherr, Frasnelli, Hummel, & Lundstrom, 2012). Our results additionally show that grey matter volume within mOFC varies positively with bitterness identification.

Table 4. Summary of the ROI analysis.

Brain Region		cluster size	peak *p*	peak T	Local maximum* x	y	z
fMRI							
COI < NC							
Medial orbitofrontal	L	76	0.04	5.10	-6	32	-18
Positive correlation with T-score							
Medial orbitofrontal	L	207	0.01	6.78	-6	32	-18
Anterior insula	L	44	0.04	4.88	-42	14	-6
Positive correlation with TDI-score							
Medial orbitofrontal	L	54	0.05	5.08	-6	32	-18
VBM							
Positive correlation with bitter d-prime							
Medial orbitofrontal	R	821	0.00	4.97	9	40	-22
	L	941	0.00	7.34	-6	24	-27

*MNI coordinates of the local maximum. Peak *p* reflects the probability of the cluster using the FWE correction for multiple tests. The cluster size is expressed in voxels. COI, congenitally olfactory impaired; NC, normosmic controls; R, right; L, left.

The mOFC is a chemosensory area involved in the hedonic perception of flavours (Rolls, Grabenhorst, Margot, Da Silva, & Velazco, 2008; Grabenhorst & Rolls, 2008), olfactory-taste learning (Rolls, 2011), processing of palatable odours (Small, Gerber, Mak, & Hummel, 2005) and sensory-specific satiation (Rolls, 2008; Pritchard *et al.*, 2008). The cluster observed in our study has been reported as pivotal structure in decision-making related to the hedonic valence of odours (Rolls, Grabenhorst, & Parris, 2010), i.e. comparing whether an odour is more or less pleasant. It is preferentially activated during extinction learning after an olfactory conditioning task (Gottfried & Dolan, 2004). Extinction happens when a response (e.g. eating) previously reinforced (e.g. hunger) is no longer effective. Extinction can be facilitated by sensory-specific satiation also known as "boredom with flavour", a phenomenon

that happens after repeated exposure to the same food. Boredom with flavour describes the decline in the perceived pleasantness of a food during its consumption. Moreover, congenitally anosmic subjects maintain their hedonic evaluation at more stable levels than normosmics (Novakova, Bojanwski, Havlicek, & Croy, 2012). Our results suggest that the lower BOLD signal observed in the mOFC of congenitally olfactory impaired might provide a neurological basis for reduced sensory-specific satiation.

4.2.Anterior Insula

The anterior insula is another region where we observed a positive correlation between the bitterness-induced BOLD signal changes and the smell performance, such that subjects that easily detected an odour activate more strongly this area when tasting bitterness.

The anterior insula is considered as the primary taste cortex (Ogawa *et al*., 2005; Veldhuizen *et al*., 2011) and plays an important role in taste intensity and pleasantness coding (Grabenhorst & Rolls, 2008; Bender, Veldhuizen, Meltzer, Gitelman, & Small, 2009; Ohla, Toepel, Le Coutre, & Hudry, 2010; Cerf-Ducastel, Haase, & Murphy, 2012), interoception and self-awareness (Bud Craig, 2009). This region also processes visceral, tactile, pain (Hummel, Iannilli, Frasnelli, Boyle, & Gerber, 2009) and olfactory information (Cerf-Ducastel & Murphy 2001; De Araujo *et al*., 2003) and is considered as a flavour-processing node (Small *et al*., 2013). Our data support the results of a previous study reporting a lower insular activity in a group of congenitally and acquired anosmic subjects compared to normosmic participants during trigeminal processing (Iannilli *et al*., 2007). Interestingly, similarly to our COI cohort, Small, Bernasconi, Bernasconi, Sziklas, & Jones-Gotman (2005b) also found elevated taste recognition and detection thresholds in a case-report study of a patient without left insula and a mild atrophy of the right insula (together with mild atrophy of left orbitofrontal cortex and severe bilateral atrophy of piriform cortex). Furthermore, Veldhuizen, Douglas, Aschenbrenner, Gitelman, & Small (2011) found that the anterior insula was more activated when subjects drank an unexpected sweet stimulus, i.e. when the taste expectation was breached. Expectations about foods tastes are ecologically acquired by visual and mainly smell information prior to ingestion. Anosmic patients who are restricted to visual food cues can be easily impaired in creating proper expectations, and therefore will be more prone to judgement

errors (Croy *et al*., 2012). It is possible that for subjects impaired in smell detection, the lack of reliable taste expectations dampens tasting-induced insular activations.

4.3.Piriform cortex

This region was not recruited by either group of subjects during tasting. The piriform cortex is the main primary olfactory area and a recent study has recently found that it processes taste information in normosmic and anosmic rats (Maier *et al*., 2012). The lack of piriform activity in our study could be explained by the duration of the olfactory impairment together with the small size of this region and/or lack of statistical power. However, our data are more in favour of the classical hierarchical view of taste-odour convergence that happens in the orbitofrontal cortex (Small *et al*., 2013). Furthermore, we show that the plasticity of a chemical sense largely differs from that of audition and vision, also known as the distal senses. Whereas the deprived "visual" cortex of congenitally blind subjects processes stimuli from other modalities like touch, hearing or olfaction (Kupers & Ptito, 2013), our data do not lend to support the hypothesis that the deprived "olfactory" piriform cortex of congenitally olfactory impaired subjects becomes invaded by taste. In the case of blindness (or deafness), cortico-cortical and thalamo-cortical connections to and from the visual (or auditory) cortex are modified in order to allow cross-modal plasticity to take place (reviews in Merabet & Pascual-Leone, 2010; Kupers & Ptito, 2013). Further studies are needed to confirm if similar adaptive structural changes, such as weaker connections between primary olfactory areas and the mOFC, also take place in the brain of isolated congenitally anosmic subjects.

5. Conclusion

In conclusion, while olfaction amplifies taste perception and taste processing, life-long olfactory impairment might have detrimental effect on this modality. This is supported by behavioral and functional imaging results. In sharp contrast with congenital blindness or congenital deafness, crossmodal plasticity does not seem to take place in congenital olfactory impairment.

Author contributions

Conceived and designed the experiments: LG, KM, HS, NT, RK, MP. Performed the experiments: LG, HGK, MV. Analyzed the data: LG, MV, KM. Wrote the paper: LG, MV, RK, MP.

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Appendix A: Supporting information

6.1 Supplementary Methods

6.1.1 MRI data acquisition

T_1-weighted images of the whole head were acquired using a 3D MP-RAGE sequence (repetition time (TR)/ echo time (TE)/ of 1.9 s/ 2.32 ms, 256x256 matrix, field of view (FoV) of 230x230, 224 sagittal slices with no gap, 0.9 mm^3 voxels). We also acquired a T_2-weighted image (TR/TE of 3.2 s/ 409 ms, 256x258 matrix and a FoV of 250x250 mm, 176 sagittal slices with no gap, interpolated voxels 0.49x0.49x1 mm^3) and a fluid attenuated inversion recovery (FLAIR) image (TR/TE/TI of 5.0 m/ 395 ms/ 1800 ms, 256x258 matrix and a FoV of 250x250, 160 sagittal slices with no gap, interpolated voxels 0.49x0.49x1 mm^3) using 3D turbo spin echo sequences.

6.1.2 Processing and statistical analysis of MRI data

We used VBM to investigate whether the taste d-prime correlate with neuroanatomical changes reported in a parallel companion study on the same dataset (in preparation).

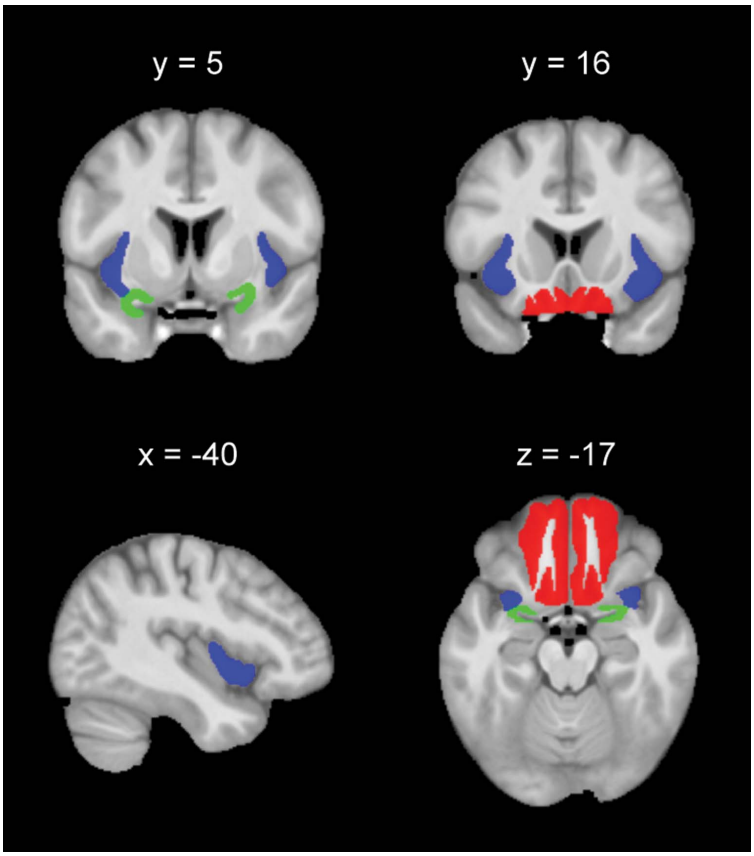
T_1-images were pre-processed and analyzed using the VBM8 toolbox in SPM8 (Wellcome Trust Centre for Neuroimaging; www.fil.ion.ucl.ac.uk/spm/). The T_1-weighted images were initially corrected for spatial distortions caused by non- linearities in the gradient

system of the scanner (Jovicich *et al*., 2006). The grey matter and white matter images were segmented in native space using the maximum a posteriori probability and partial volume estimation method, including estimation of parameters for affine transformation to standard MNI space for the modulation procedure. A study specific template was calculated based on the grey and white matter tissue maps using high-dimensional non-linear warping in DARTEL (diffeomorphic anatomical registration through exponentiated lie algebra) (Ashburner, 2007). The study specific template was normalized to the Montreal Neurological Institute (MNI) space and the tissue maps were warped to the study specific MNI template. Finally, the warped tissue maps were modulated using the Jacobian determinant of the applied deformation fields to correct for local volume changes following the high dimensional inter-subject warping. The modulated grey matter tissue maps were smoothed with a 6 mm Gaussian kernel. An average T_1 template was calculated based on all subjects' DARTEL warped T_1 images. A binary grey matter mask was acquired from the study specific DARTEL template and thresholded at 0.3. The mask was applied for the VBM analyses to exclude voxels with low grey matter probability.

To test if taste performance correlated with grey matter volume, we analyzed both groups combined in a whole-brain multiple regression analysis entering the d-primes for the taste identification scores as the covariate of interest, controlling for age and gender (Van Laere *et al*., 2001). The whole-brain t-value maps were thresholded at $p \leq 0.001$ uncorrected and significance was assessed at the cluster level applying a statistical threshold of $p \leq 0.05$ and family-wise error (FWE) correction to control for multiple comparisons as implemented in SPM8. For the pre-defined ROIs, FWE correction only considered the voxels within the ROIs, applying the same statistical criteria for defining statistical significance.

6.1.3.Regions of interest

Three ROIs (Supplementary Figure 1) were drawn in the bilateral mOFC, piriform cortex and anterior insula on the average T_1 template using FSLview (http://fsl.fmrib.ox.ac.uk/fsl/fslview/). The ROIs were defined according to the human brain atlas of Duvernoy (1999) and Mai (1997). The mOFC included the medial orbital gyrus and the gyrus rectus, posteriorly delineated at the olfactory trigone and anteriorly including the frontal pole. Medially, the superior border was defined at the supraorbital sulcus. The anterior



Supplementary Figure 1. Anatomical region of interest (ROIs) drawn in bilateral medial orbitofrontal cortex (red), anterior insula (blue) and piriform (green) cortices. The ROIs are displayed on the group template. The right hemisphere corresponds to the right of the image.

insula included the three short insular gyri with the posterior border demarcated by the insular sulcus. The superior border was defined by the circular insular sulcus and the falciform fold defined the inferior border. The piriform cortex included a frontal and a temporal segment. The anterior border of the frontal piriform cortex was defined at the olfactory trigone posterior to the mOFC ROI. Medially, the frontal piriform cortex segment was delineated at a vertical line drawn from the medial border of the temporal lobe (posteriorly uncus). The lateral border of the frontal piriform cortex was defined at the insula gyrus until separated by the junction of the frontal and temporal cortex (limen insulae) demarcating the anterior border of the temporal piriform cortex. The temporal piriform cortex was delineated medially at the uncus and included the periamygdaloid cortex in the posterior segments. The posterior border of the

temporal and frontal piriform cortex was demarcated when the semiannular sulcus emerged as a small protrusion.

Supp Table 1. Lower BOLD signal in COI < NC for SWEET > SOLVENT.

Brain Region		BA	MNI coordinates			cluster	peak	peak
			x	y	z	size	*p*	T
Frontal lobe								
Inferior orbitofrontal	L	38	-32	24	-22	32	0.88	6.32
Superior frontal	L	8-10	-20	14	42	16	0.97	4.69
Precentral	L	6	-32	-2	42	12	0.98	5.94
Supplementary motor area	R	6	8	-12	70	1	0.99	3.78

Peak *p* reflects the probability of the cluster using the FWE correction for multiple tests. The cluster size is expressed in voxels. COI, congenitally olfactory impaired; NC, normosmic controls; MNI, Montreal Neurological Institute; R, right; L, left; BA, Brodman area.

6.2.Supplementary imaging results

Supplementary tables 1 and 2 list the lower BOLD signal in congenitally olfactory impaired compared to control subjects for sweet and salty. The ROI analysis further confirmed the absence of a significant group difference in mOFC, anterior insula and piriform cortices.

Supp Table 2. Lower BOLD signal in COI < NC for SALTY > SOLVENT.

Brain Region		BA	MNI coordinates			cluster	peak	peak
			x	y	z	size	*p*	T
Frontal lobe								
Superior frontal	L	8	-20	22	58	45	0.78	5.89
Temporal lobe								
Inferior temporal	R	20	54	-32	-14	9	0.98	4.29
Cerebellum	R		10	-44	-24	1	0.99	3.89

Peak *p* reflects the probability of the cluster using the FWE correction for multiple tests. The cluster size is expressed in voxels. COI, congenitally olfactory impaired; NC, normosmic controls; MNI, Montreal Neurological Institute; R, right; L, left; BA, Brodman area.

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Article 5

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Making sense of the chemical senses

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Abstract

We review our recent behavioural and imaging studies testing the consequences of congenital blindness on the chemical senses in comparison with the condition of anosmia. We found that congenitally blind (CB) subjects have increased sensitivity for orthonasal odorants and recruit their visually deprived occipital cortex to process orthonasal olfactory stimuli. In sharp contrast, CB perform less well than sighted controls in taste and retronasal olfaction, i.e. when processing chemicals inside the mouth. Interestingly, CB do not recruit their occipital cortex to process taste stimuli. In contrast to these findings in blindness, congenital anosmia is associated with lower taste and trigeminal sensitivity, accompanied by weaker activations within the "flavour network" upon exposure to such stimuli. We conclude that functional adaptations to congenital anosmia or blindness are quite distinct, such that CB can train their exteroceptive chemical senses and recruit normally visual cortical areas to process chemical information from the surrounding environment.

Keywords: Blindness, anosmia, smell, taste, trigeminal, flavour.

1. Introduction

Sensing chemicals in the environment is likely the oldest modality in the history of life, allowing unicellular organisms to guide themselves towards food sources by chemotaxis. In the course of evolution, multicellular animals have developed more complex sensory systems, allowing them to extend their perceptual reach. For example, sight allows animals to identify and hunt prey species located between themselves and, ultimately, the horizon. When an individual approaches a possible food source, it gradually comes to perceive additional and supplementary characteristics by virtue of proximal vision, as well as other sensory modalities responsive to sounds, smells, and temperature. Importantly, among vertebrates, it is only when food items enter the buccal cavity that the perceptual reach of vision normally ceases to overlap with the chemical senses. In this review, we first summarise the existing literature on sensory trade-offs in phylogeny between vision and the chemical senses. We then proceed to give an account of the sensory and cross-modal consequences of visual deprivation on chemosensory perception and processing that arise from neuronal plasticity. Finally, we compare the effects of visual deprivation on analogous effects of olfactory deprivation, which have only recently come to be appreciated.

2. Sensory Trade-Offs During Evolution

Olfaction in mammals can be divided in two sub-systems: the main olfactory system (MOS), and the accessory olfactory system (AOS). The vomeronasal organ of the AOS responds to social odorants such as pheromones or vasanas (McClintock, *et al*., 2001; Meredith, 2001), which entails direct contact between chemicals dissolved in body fluids and the vomeronasal organ (Keverne, 1999). The AOS is facilitated by stereotypic behaviour such as flehmen, directing liquids to the sensory epithelium (Rajanarayan and Archunan, 2004). Among mammals, the relative size of the main olfactory bulb (MOB) correlates with diet and activity period, whereas the size of the accessory olfactory bulb (the AOB, which subserves the AOS) varies with social and mating systems (Barton, 2006). For example, the size of the MOB is larger in nocturnal monkeys than in diurnal species, and likewise in frugivores and insectivores compared to folivores (Barton, 2006). Furthermore, it has been argued that trichromatic vision in monkeys, allowing discrimination of red and green colors, has evolved

to insure optimal leaf (rather than fruit) consumption in primates, i.e. by allowing selection of young leaves with high protein levels and low toughness (Dominy and Lucas, 2001). On the other hand, the AOS is vestigial and the signal transduction pathway for pheromones is impaired in *catarrhini* primates, i.e. old world monkeys, great apes and humans (Barton, 2006; Zhang and Webb, 2003). Such relative poverty of olfactory function is accompanied by a major loss of olfactory receptor (OR) genes; while approximately 20% of the OR genes contain loss-of-function mutations in mouse and dog, this percentage rises to 30% for non-human apes, and attains almost 60% in humans (Gilad *et al*., 2004). Interestingly, this significant reduction in the olfactory repertoire occurs in all monkeys that possess trichromatic vision in both males and females, i.e. the old world monkeys and the new world howler monkey (Gilad *et al*., 2004). Inheritance of trichromacy in male primates allows recognition of the ovulation period in females with oestral swelling and reddening of the perineum. In humans, trichromacy facilitates recognition of emotions conveyed by facial blushing. This is analogous to the case of avians, which lack a vomeronasal organ but possess tetrachromatic vision, and of which males typically display colourful feathers to females prior to mating (Keverne, 1999; Zhang and Webb, 2003). Thus, vision seems to have evolved at the expense of olfaction, presumably by usurping some of its functions.

As for olfaction, trade-offs between gustation and vision also occur. However, the available literature seems mainly to be limited to animals that live underwater. For example, when compared to its sighted morph living close to the surface, the blind cave-dwelling fish *Astyanax Mexicanus* possesses an enhanced feeding apparatus, including an increased number of taste buds combined with a wider and more protruding lower jaw (Jeffery, 2001; Varatharasan *et al*., 2009). The nerve fibre plexus of its taste buds also contains more axons than that of sighted cousins (Boudriot and Reutter, 2001). Interestingly, early surgical lens ablation in the sighted morph increases the number of teeth on the lower jaw (Dufton *et al*., 2012), suggesting epigenetic factors in the trajectory of development of sensory systems.

For species living in an aerial environment, the impact of loss of sight is different than for fishes. For example, mammals such as bats, that generally rely more on audition than on vision, lack the taste receptor gene *Tas1r1*, responsible for sensing umami (Jones *et al*., 2013; Zhao *et al*., 2012). Interestingly, this reduced taste perception occurs regardless of the diet and affects equally fructivores, insectivores, and blood feeders. Moreover, new world vampire bats

lack two other taste receptor genes, *Tas1r2* and *Tas1r3*, required for perception of both umami and sweetness (Zhao *et al*., 2012). This indicates that animals living in an aqueous environment enjoy enhancement of gustation with loss of vision, whereas species living in an aerial environment suffer a decline in gustatory sense when vision is reduced.

3. Cross-Modal Plasticity in Congenital Blindness

In humans, congenital blindness has tremendous effects on the remaining sensory modalities. Visual processing areas occupy almost one-third of the total cortical surface, leaving to congenitally blind subjects a large unoccupied cortical territory that can be used by other sensory modalities (review in Kupers and Ptito, 2014). We now review the effects of congenital blindness on the chemical senses and highlight the differences between types of chemo-sensation that involve the perception of chemicals presented outside and inside the body.

3.1. Olfaction

Olfaction provides information about chemicals present in the environment and also arising from the body. Inhalation of odorants through the nostrils is referred to as orthonasal olfaction, whereas perceiving odours through the nasopharynx during exhalation, mastication and swallowing is considered as retronasal olfaction (Bojanowski and Hummel, 2012). While the former type of olfactory perception relies upon the wind to bring chemicals to the nose, the latter type mainly occurs during feeding, with the precondition that the subject has decided to place a food inside his mouth.

3.1.1. Behavioural Studies on Orthonasal Olfaction

Several studies report that orthonasal olfactory perception is enhanced in people who have lost their sight early in life. Using the odour awareness scale (Smeets *et al*., 2008), our group has shown that congenitally blind subjects have an increased odour awareness compared to their sighted counterparts (Fig. 1A, Beaulieu-Lefebvre *et al*., 2011), especially with regard to self-hygiene odours and perfumes. For example, the blind report noticing quickly new fragrances, aftershaves or deodorants worn by their friends, and also to paying particular

attention to odours inside someone else's house, or evaluating carefully the perfume of a soap or detergent before buying it, etc. Objective methods also demonstrate a heightened sensitivity of the orthonasal sense of smell in the visually impaired, although some literature reports fail to find significant group differences (Luers *et al*., 2014; Schwenn *et al*., 2002; Smith *et al*., 1993). For example, blind subjects detect butanol at lower concentrations compared to blindfolded sighted participants (Fig. 2A; Beaulieu-Lefebvre *et al*., 2011; Cuevas *et al*., 2010). Furthermore, the ability to discriminate (Cuevas *et al*., 2009) and correctly name odours from everyday life (e.g. pipe tobacco, leather, ketchup, etc.) is increased in blind adults (Cuevas *et al*., 2009; Murphy and Cain, 1986) and children (Rosenbluth *et al*., 2000); the heightened olfactory perceptions are notable when participants are asked to name an odour without being given any cues. Wakefield *et al*. (2004) have suggested that the blind's superiority in olfaction is related to improved cognitive skills involving non-visual memory and attention.

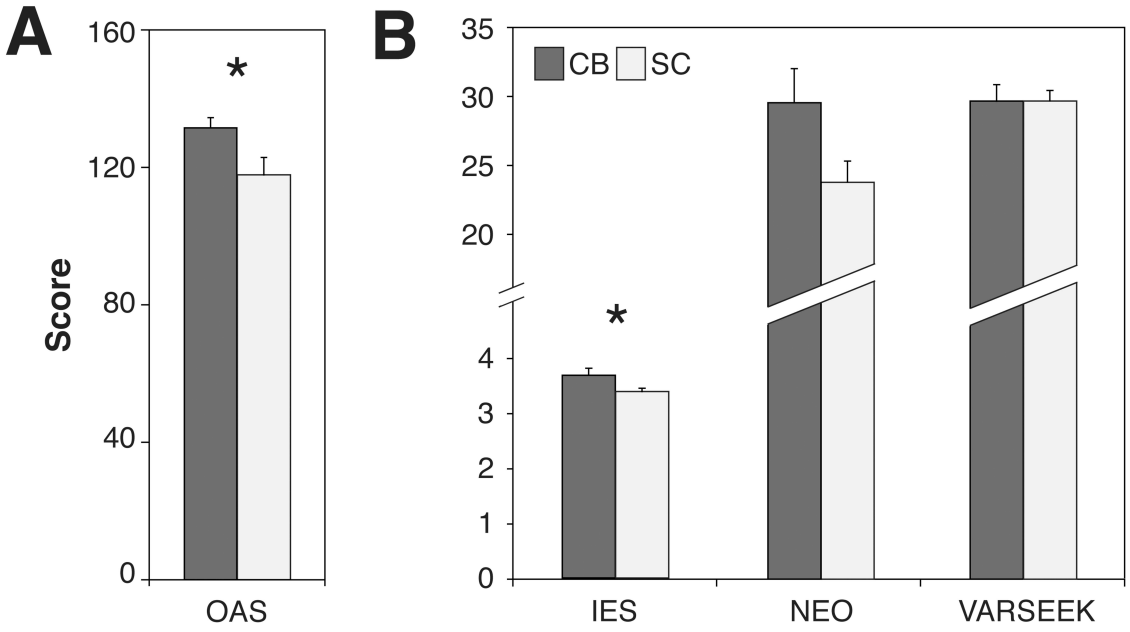

Figure 1. Higher olfactory awareness **(A)** and intuitive eating **(B)** scores in congenitally blind (CB) compared to sighted control (SC) subjects. **(A)** Odour Awareness Scale (OAS) scores showing higher odour awareness in CB (n = 14) compared to SC (n = 11) subjects. **(B)** Eating habit questionnaires showing higher intuitive eating attitude in CB (n = 26) compared to SC (n = 17); food neophobia and variety-seeking tendency did not differ. Abbreviations: OAS, Odour awareness scale; IES, Intuitive eating scale; NEO, Food neophobia scale; VARSEEK, Variety seeking tendency scale. The bar charts display mean ± standard error of the mean (SEM); $*p < 0.05$.

3.1.2. Behavioural Studies on Retronasal Olfaction

Given that retronasal olfaction depends upon the experience of feeding, which, as argued in the next section, is negatively affected by lack of vision (Bilyk *et al*., 2009), we tested the hypothesis whether retronasal olfactory performance of congenitally blind is worse than that of sighted controls, despite the former having enhanced orthonasal olfactory abilities (Gagnon *et al*., in prep. a). We used Heilman *et al*.'s protocol (2002), but extended the original stimulus list to include food powders that could deliver odorants *via* both olfactory routes. As illustrated in Fig. 2B, our results showed that when participants are asked to name the food powder by sniffing through their nostrils, the blind tended to perform better compared to blindfolded sighted controls. However, when trying to identify the food retronasally, the blind lost their advantage, tending to perform worse than their sighted counterparts, such that there was a significant group x olfactory route interaction.

3.1.3. Imaging Studies

When deprived of visual inputs since birth, the brain shows a remarkable adaptive cross-modal plasticity in allowing the visually deprived cortex to process information arising from other senses (reviews in Kupers *et al*., 2011a; Kupers and Ptito, 2011, 2014). So far, only one imaging study has investigated the neural correlates of (orthonasal) olfactory processing in blindness (Kupers *et al*., 2011b), and data on retronasal olfaction are currently missing. Similarly to cases of audition (Gougoux *et al*., 2009; Lewis *et al*., 2011) and touch (Amedi *et al*., 2010), orthonasal olfactory processing recruits more strongly the occipital cortex in the blind, compared to blindfolded sighted participants (Fig. 3A; Kupers *et al*., 2011b). Other regions with heightened activity include conventional olfactory regions such as the right amygdala, right lateral orbitofrontal cortex and bilateral hippocampi. Given that the right lateral orbitofrontal cortex mediates conscious olfactory perception (Li *et al*., 2010), whereas the hippocampus is a pivotal region involved in memory, these findings offer a neuronal underpinning of the blind's increased odour awareness and/or odour memory (Kupers *et al*., 2011b).

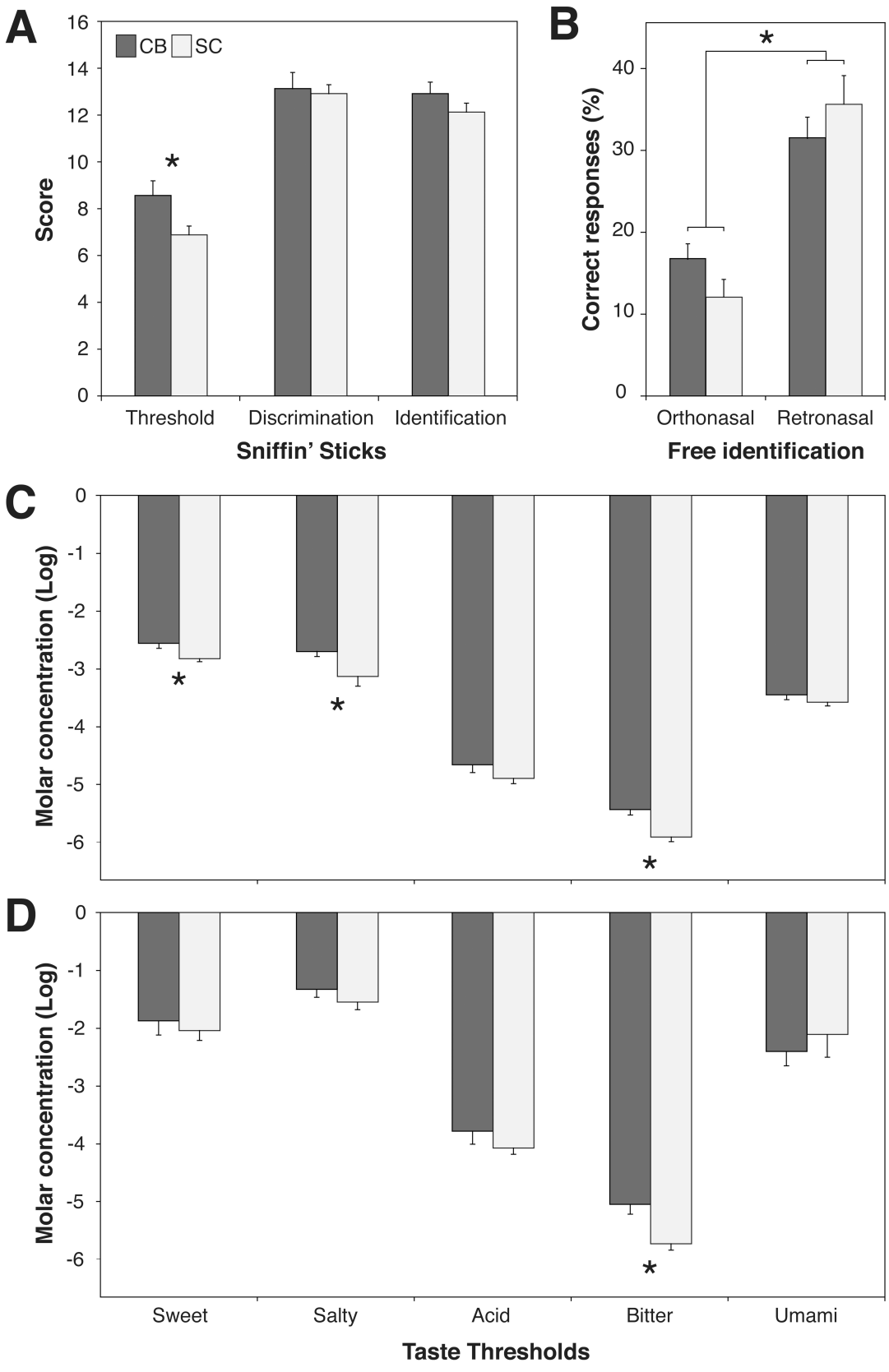
A
CB
SC
Score
16
14
12
10
8
6
4
2
0
*
Threshold
Discrimination
Identification
Sniffin' Sticks
B
*
Correct responses (%)
40
30
20
10
0
Orthonasal
Retronasal
Free identification
C
Molar concentration (Log)
0
-1
-2
-3
-4
-5
-6
*
*
*
D
Molar concentration (Log)
0
-1
-2
-3
-4
-5
-6
*
Sweet
Salty
Acid
Bitter
Umami
Taste Thresholds

Figure 2. Chemosensory performance in congenitally blind (CB) individuals. **(A)** Sniffin´ Sticks Threshold-Discrimination-Identification (TDI) sub-scores showing lower detection threshold in CB (n = 11) compared to sighted control (SC, n = 14) subjects. **(B)** Significant group x olfactory route interaction showing that CB (n = 12) tend to perform better than SC (n = 14) subjects at identifying orthonasal odorants, but tend to perform worse when identifying odours retronasally. **(C-D)** Significant group effect showing higher taste detection **(C)** and identification **(D)** thresholds in CB (n = 11) compared to SC (n = 13). The bar charts display mean ± SEM; *$p < 0.05$; adapted from Beaulieu-Lefebvre *et al.* (2011) **(A)** and Gagnon *et al.* (2013) **(C, D)** with permissions of Elsevier **(A)** and Oxford University Press **(C, D)**.

3.2. Taste

The sense of taste provides information not only about contact between objects from the external world and the inner body, but also about the fusion or reunion of the external world with the inner body. Taste signals from the tongue, which are conveyed by the facial (VII) and glossopharyngeal (IX) nerves, assess the (lack of) edibility of objects prior ingestion. The tongue is considered to respond to at least five basic tastants; i.e. sweet, salty, acid, bitter and umami (Scott, 2005). However, gustation is not restricted to these tastants alone, and taste receptors are also found inside the body, especially within the gastro-intestinal tract (Trivedi, 2012). Importantly, our sense of taste tracks the post-ingestive consequences of a food, and informs learning about its beneficial and detrimental effects, such as energy gain or uncomfortable visceral distensions (Miranda, 2012), therefore aiding survival of the organism. Three parallel anatomical pathways are thereby involved, which process the sensory, hedonic and visceral aspects of the gustatory sensoria (Sewards, 2004). Interestingly, as the taste system overlaps with the central pain pathway, Craig (2002, 2003), has suggested that it is actually part of a larger interoceptive network, involving the lamina I spino-thalamocortical pathway, which provides an array of sensory inputs contributing to subjective feelings, emotions and self-awareness.

The role of vision is undoubtedly important in tasting. Not only does sight guide food search and selection, and facilitate meal preparation, vision also creates expectations about the foods we eat. These expectations, that are acquired and refined through feeding experience, are strongly encoded in our memory, such that they can influence our desire to eat, and modulate taste perceptions. For example, simply adding a tasteless colorant to water can elevate or lower taste thresholds, even when participants were warned that the color is irrelevant information (review in Spence *et al*., 2010). Taste perception can therefore be easily

manipulated by altering either appearance (Wheatley, 1973; see also Liang *et al*., 2013) or descriptive labels (Crum *et al*., 2011; Levitan *et al*., 2008; Yeomans *et al*., 2008) of foods. More interestingly, the mindset of expectations about foods and their visual presentation activate the gustatory cortices, i.e. the insula/operculum and orbitofrontal cortex, even in the absence of gustatory stimulation (Barros-Locertales *et al*., 2011; review in Van der Laan *et al*., 2011). Therefore, it is clear that visual input primes the gustatory cortex prior to food ingestion, allowing the brain and body to prepare and respond optimally (Crum *et al*., 2011; Feldman and Richardson, 1986; Powley, 2000).

3.2.1. Behavioural Studies

Unsurprisingly, the loss or congenital absence of vision has dramatic consequences on feeding behaviour. Visually impaired subjects encounter various blindness-related obstacles when searching for foods, preparing meals, or eating out in restaurants (Bilyk *et al*., 2009). For example, packaging inherently limits availability of tactile and olfactory information about foods, and description of the package contents is rarely provided in Braille. Moreover, the lack of reliable and knowledgeable assistance in supermarkets often creates frustration during grocery shopping. When blind subjects do shop for food, their choice of groceries is often based on a memorised list of items, rather than on a spontaneous desire to buy according to attractive packaging or colors and texture of food items. Cooking also presents many threats for the blind, including the use of hot stoves and sharp knives (Kutintara *et al*., 2013). When eating out in restaurants, the menus are rarely available in Braille, which increases the dependence of the blind population on sighted friends and waiters. As a result, blind subjects understandably feel discouraged about shopping and cooking, and their diet accordingly suffers from a lack of variety (Bilyk *et al*., 2009).

One interesting study on the role of vision on feeding behaviour (Linne *et al*., 2002) reports that when eating a commercially prepared dish of diced meat, onions and potatoes, blindfolded sighted people eat less and more slowly than when they eat the same meal with full vision. Such results were partially replicated in a real dining-in-the-dark restaurant setting (Scheibehenne *et al*., 2010). Moreover, congenitally blind subjects eat slower than their sighted counterparts without blindfold (Linne *et al*., 2002). This could present an advantage

for the blind, since eating slowly is associated with a more pronounced postprandial anorexigenic hormonal release (Kokkinos *et al*., 2010) that contributes to satiety.

Due to these blindness-related obstacles when eating, the sense of taste is likely to suffer in subjects with low vision. Importantly, we have shown that taste sensitivity is lowered in congenital blindness (Gagnon *et al*., 2013), making gustation the only remaining sensory modality in which the blind do not outperform the sighted. Indeed, taste detection and identification thresholds are significantly elevated in congenitally blind subjects compared to blindfolded sighted controls, as illustrated in Fig. 2C and 2D. Our group further demonstrated that congenitally blind subjects have a better intuitive eating attitude (Tylka, 2006) compared to sighted subjects (Gagnon *et al*., 2013), a finding that was replicated by compiling data from our Danish and Canadian samples (Fig. 1B). For example, the visually impaired listen more to their internal hunger and satiety cues, and eat more for physical than emotional reasons compared to the sighted. Moreover, they seek as much variety in their diet as do the sighted (Fig. 1B), although they may not succeed as well in this regard (Bilyk *et al*., 2009). Blind subjects have a trend towards greater neophobia about unfamiliar foods. Overall, these data indicate that, despite a certain lack of variety in their diet, the blind are as just as interested (as the sighted) in trying out new food products or ethnic dishes, and obtaining a varied diet. This should encourage caregivers and rehabilitation professionals to introduce people with visual impairments to cooking and gastronomy classes.

3.2.2. Imaging Studies

We have recently investigated whether cross-modal plasticity develops between vision and gustation in congenital blindness (Gagnon *et al*., in prep. b). Based upon the blind's reduced gustatory performance in detecting and identifying tastants (Gagnon *et al*., 2013), and functional imaging studies showing correlations between occipital activity and sensory performance (Amedi *et al*., 2003; Gougoux *et al*., 2005; Ptito *et al*, 2005; Renier *et al*., 2013), we hypothesized that congenitally blind would not recruit their occipital cortex to process taste information. Functional magnetic resonance imaging (fMRI) during a task requiring the rating of the intensity or pleasantness of tasty (sweet, bitter) and tasteless (artificial saliva) liquids showed blood-oxygen-level dependant (BOLD) signal increases in both blind and sighted groups in the left primary taste and somatosensory cortices in response to tastants compared to

saliva. However, the taste stimuli (compared to saliva) activate less strongly the right posterior insula and overlying operculum together with the bilateral hypothalamus of the blind group compared to the sighted group (Fig. 4A). More importantly, the blind did not recruit their visually deprived occipital cortex while tasting (Fig. 3B), such that there was no BOLD signal difference there between blind and sighted people performing the sensory task. These findings contrast sharply with corresponding imaging studies on olfaction (Fig. 3A; Kupers *et al*., 2011b), audition (Gougoux *et al*., 2009; Lewis *et al*., 2011) and touch (Amedi *et al*., 2010; Ptito *et al.*, 2005), all of which have highlighted the recruitment of the deprived visual cortex of the blind in processing information arising from another modality. This can be excluded for the case for taste since blind people do not manifest superior tasting abilities, and do not recruit their visual cortex in response to tastants.

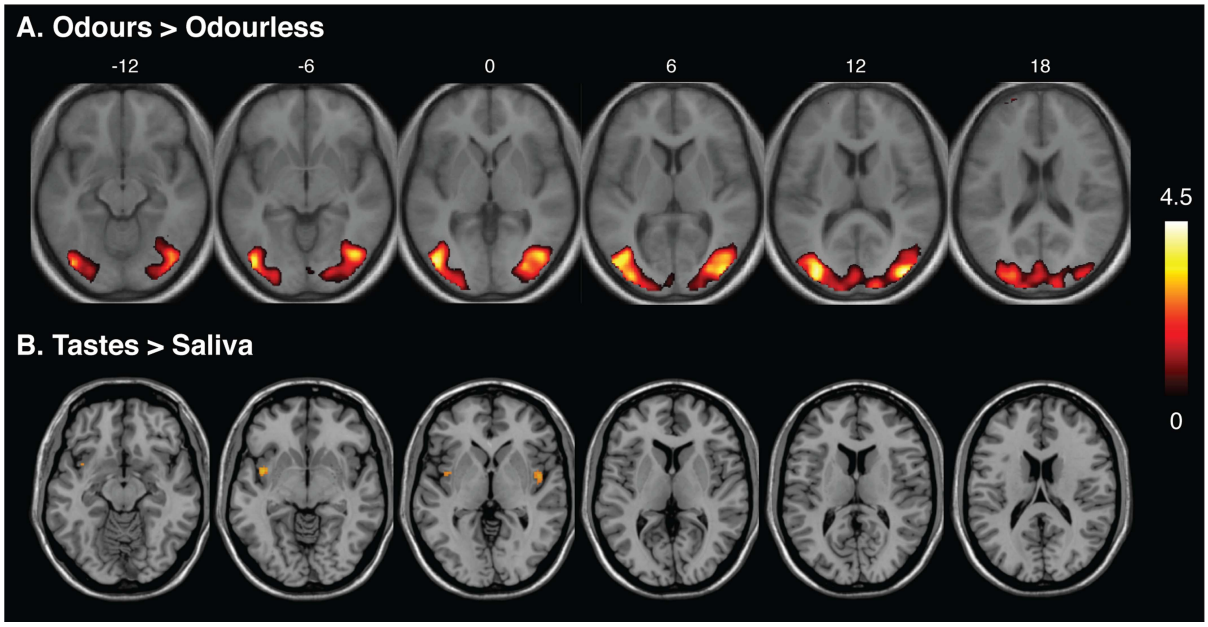

Figure 3. BOLD responses to smell **(A)** and taste **(B)** in congenitally blind (CB) individuals. **(A)** CB (n = 14) recruit their occipital cortex when detecting an odorant compared to the odourless solvent. **(B)** CB (n = 9) do not recruit their occipital cortex when rating the pleasantness or intensity of tastes (sweet + bitter) compared to tasteless artificial saliva. The z coordinate of the slices refers to the axial plane in the Montreal Neurological Institute (MNI) space. Activation maps with the visualization threshold set at $p < 0.01$ (uncorrected), are displayed on the group template **(A)** or ch2 template provided by MRIcron **(B)**. The right hemisphere corresponds to the right of the image. Adapted from Kupers *et al.* (2011b) with permission of Elsevier **(A)**. This figure is published in colour in the online version.

3.3. Trigeminal Chemosensation

The trigeminal nerve (cranial nerve V) is divided into three main branches, i.e. the ophthalmic (V1), maxillary (V2) and mandibular (V3) that together innervate the face, including the nasopharynx and oral cavity. Sensory branches from V1, V2 and V3 convey thermal (warm, cold), tactile (textures, viscosity), painful (chilli's pungency) and non-painful (red wine's astringency, mint's freshness) trigeminal sensations, while the motor branches mediate the activation of the mastication musculature (V3, Borsook *et al*., 2003; Gillig, 2010). It is generally difficult to dissociate trigeminal sensations from odour (e.g. eucalyptus) or flavour (e.g. chilli) sensations, since relevant stimuli almost always activate two chemical senses simultaneously. Most odorants activate the trigeminal nerve in a concentration-dependent manner when administered orthonasally. Although very few studies have investigated pure trigeminal sensitivity in congenitally blind people, one must keep in mind that orthonasal olfaction studies tend to include bimodal odorants with trigeminal qualities (e.g. mint) to assess the so-called general olfactory sensitivity (e.g. Sniffin' Sticks battery).

Only a very few human studies have assessed pure intranasal trigeminal chemosensation in the blind, and we are not aware of any investigations of intraoral trigeminal sensitivities. Available studies are limited to electroencephalographic experiments measuring trigeminal event-related potentials evoked by the pure trigeminal stimulus carbon dioxide (CO_2). Both Cuevas *et al*. (2011) and Schwenn *et al*. (2002) failed to find differences between blind and sighted subjects in latencies, amplitudes or topographical distribution of electrocortical responses. More importantly, early blind did not show a larger recruitment of their occipital lobe compared to sighted controls (Cuevas *et al*., 2011). However, since the authors also failed to find group differences in occipital activity upon stimulating the nose with a pure olfactory odorant, they speculated that their negative results reflect the simplicity of the task consisting of passive stimulation, i.e. without a cognitive component.

3.4. Summary

We conclude that when congenitally blind subjects perceive unimodal chemosensory stimuli originating outside their body, such as orthonasal odours (Beaulieu-Lefebvre *et al*., 2011), they show a behavioral advantage over blindfolded sighted subjects. This advantage is associated with a cross-modal plastic response involving recruitment of the deprived visual

cortex together with a general increased activity of chemosensory processing areas compared to normal sighted (Kupers *et al*., 2011b). However, when blind individuals process chemosensory stimuli located inside their body, such as sweet, bitter and other basic tastes (Gagnon *et al*., 2013) and retronasal odours (Gagnon *et al*., in prep. a), they perform worse than normal sighted subjects. More importantly, blind individuals do not recruit additional occipital cortex and activate less strongly the usual chemosensory areas compared to sighted controls in response to simple foods in their mouth (Gagnon *et al*., in prep. b).

Together, these findings indicate that cross-modal plasticity involving vision and the chemical senses depends also on the spatial location of the perceived stimulus, i.e. whether it is located inside the body (mouth, digestive tract) or in the external world. Therefore, compensatory mechanisms (such as heightened sensitivity and cross-modal recruitment of additional cortex) involving the chemical senses seem to occur in congenital blindness only if they can emulate visual functions, i.e. perceiving objects at a distance from or in contact with the body (e.g. orthonasal odours). For chemical senses implicated in flavour perception of foods placed in the mouth (i.e. taste, retronasal odours), no compensation for loss of vision is evident and sensitivity of chemosensory perceptions is negatively affected. Furthermore, the normal chemosensory processing areas are less activated in the visually deprived brain.

4. Cross-Modal Plasticity in Congenital Anosmia

The sense of smell occupies a relatively small cortical surface area compared to vision (Barton, 2006). More importantly, olfactory processing areas in the normosmic (normal smelling) brain largely overlap with taste and trigeminal cortices, which form the flavour network (Lundstrom *et al*., 2011). This means that, unlike blind people, anosmics do not possess a large volume of sensory-deprived cortex that can be used by other senses.

The impact of loss of olfaction is often underestimated in the general population. Anosmia and hyposmia, respectively defined as the absence of useful olfactory perception or a general decrease in olfactory function, negatively affect quality of life, especially regarding feeding, perception of environmental hazards, as well as social relationships and communication (Croy *et al*., 2012a, b; Novakova *et al*., 2012). For example, pleasantness evaluations of common foods, such as banana, are higher in congenital anosmic compared to

normosmic subjects (Novakova *et al*., 2012). Interestingly, while normal subjects decrease their pleasantness ratings of a banana the more they eat of it, congenitally anosmics maintain their hedonic evaluations more steadily during consumption. This indicates the occurrence of reduced sensory-specific satiety (Novakova *et al*., 2012). Moreover, the loss of smell at birth apparently leads to deficits in social interactions, such that congenitally anosmics have fewer sexual partners throughout their life, increased risk of household accidents, and increased risk of depressive symptoms (Croy *et al*., 2012a, b). Studies in acquired anosmia further underline the importance of the sense of smell in enjoying the eating experience. Similarly to sight, olfaction contributes to building up expectations and appreciation of the foods' variety of flavours. With acquired anosmia later in life, subjects show reduced appetite and lower interest in eating, lose or gain body weight, and experience affective disturbances together with a generally decreased quality of life (Aschenbrenner *et al*., 2008; Ferris *et al*., 1985; Mattes and Cowart, 1994; Miwa *et al*., 2001; Temmel *et al*., 2002; Van Toller, 1999). Many acquired anosmics complain that foods all taste the same (e.g. both apple and chocolate taste merely sweet), and rehabilitation professionals encourage them to prepare foods with ingredients that contrast in temperatures, textures, and other trigeminal sensations. We report in the following sections the effects of congenital and acquired anosmia or hyposmia on the remaining chemosensory modalities, i.e. gustation and the trigeminal sense.

4.1. Taste

4.1.1. Behavioural studies

Behavioural studies investigating taste sensitivity in congenital olfactory impaired subjects are scarce, given the low prevalence of the condition, which affects only 0.05 % of the general population (Karstensen and Tommerup, 2011). Hasan *et al*., (2007) found similar electrogustometric thresholds in patients with congenital anosmia due to Kallman syndrome and healthy normosmic subjects, although this negative result could easily be attributed to their low samples size of only four subjects per group. In contrast, Levy and colleagues (2013) found that nearly half of their congenital anosmia patients (n = 40) exhibited lower taste detection and identification skills compared to normosmic subjects, especially regarding bitter. Similarly, Landis *et al*., (2010) detected lower taste identification performance in a mixed group of mostly acquired olfactory impairment compared to normosmic subjects. Moreover,

experimentally induced obstruction of the olfactory cleft for one hour did not affect gustatory performances in normosmic subjects (Landis *et al*., 2010). In functionally anosmic patients, Yang *et al*. (2012) measured lowered gustatory identification sensitivity compared to normosmic controls. We recently obtained similar findings in a group of congenitally olfactory impaired subjects, who also performed worse than normosmic controls when asked to recognize bitter compared to other tastants, such as sweet, salty and (control) water (Gagnon *et al*., 2014). The literature on acquired anosmia points towards similar negative consequences of the absence of smell upon taste perception. For example, Gudziol and colleagues (2007) measured lower taste detection and identification thresholds in acquired anosmic subjects compared to normosmic controls. Taken together, these findings indicate that olfactory impairment is often, if not always, accompanied by a decreased ability to taste.

4.1.2. Brain imaging studies

The taste system overlaps with olfactory processing areas. Human imaging studies on bimodal flavour (taste and retronasal smell) processing have demonstrated that taste-odour convergence occurs in the amygdala, as well as in the primary and secondary taste cortices (De Araujo *et al*., 2003, review in Small and Prescott, 2005), i.e. the insula/operculum and orbitofrontal cortex ('classical hierarchical view'; Small *et al*., 2013). However, a recent electrophysiological study of acquired anosmic rats found taste response within the posterior piriform cortex (Maier *et al*., 2012), which suggests an earlier convergence site of taste and olfactory information ('emerging view'; Small *et al*., 2013). In order to test which taste-odour integration view best applies in humans, we recently investigated taste processing in members of a congenitally olfactory impaired family from the Faroe Islands using fMRI (Gagnon *et al*., 2014). Results showed that the lower bitterness identification abilities observed in our congenitally olfactory impaired subjects were associated with a lower tasting-evoked neural response within the medial orbitofrontal cortex, and a similar tendency towards attenuated activation within the bilateral insulae/opercula compared to normosmic controls (Fig. 4B). Interestingly, no group difference in brain activity while tasting was found within the piriform cortex, indicating that our results better support the classical hierarchical view of taste-olfactory convergence.

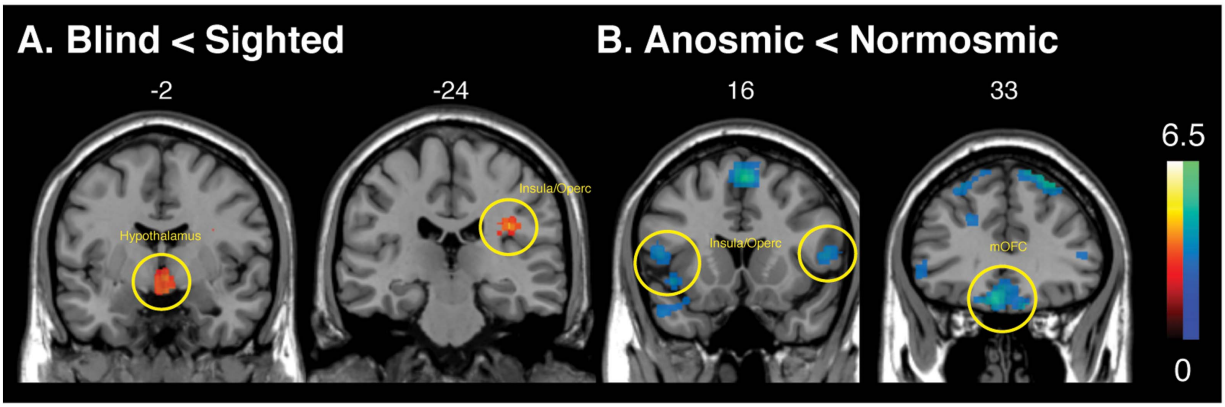

Figure 4. Lower taste responses in CB and congenitally olfactory impaired (COI) subjects. **A**) CB (n = 9) recruit less strongly than SC (n=14) subjects the hypothalamus and right posterior insula and overlying operculum. **B**) COI (n = 12) recruit less strongly than normosmic controls (NC, n = 8) the bilateral insulae/opercula and medial orbitofrontal cortex. The y coordinate of the slices refers to the coronal plane in the MNI space. Activation maps with the visualization threshold set at $p < 0.01$, $k < 80$ (uncorrected), are displayed on the ch2 template provided by MRIcron. The right hemisphere corresponds to the right of the image.

4.2. Trigeminal Chemosensation

Trigeminal chemosensation, the third complementary sensory modality of the flavour network, allows, together with taste and retronasal olfaction, a full appreciation of foods reaching the mouth. This modality interacts early with the taste system at the level of the nucleus of the solitary tract in the medulla and lower pons. It continues to overlap with central taste, and later smell, processing areas until attaining the insula and orbitofrontal cortices (Craig, 2002; Lundstrom *et al*., 2011), i.e. where the perception of flavours is formed, with additional projections to the primary somatosensory cortex.

4.2.1. Behavioural Studies

Using formic acid in a lateralisation task to assess trigeminal sensitivity, Gudziol and colleagues (2001) found increased irritation thresholds in a large cohort of acquired anosmic patients compared to normosmic controls. Interestingly, these authors measured trigeminal perceptual differences between anosmics suffering from various aetiologies, such as head trauma, which typically results in greater impairment than does sinonasal disease. The behavioral findings were partly replicated by Frasnelli *et al*. (2006, 2007a, 2010) and Ren *et*

al. (2012) who showed a higher CO_2 detection threshold in a group of (mainly) acquired olfactory impaired subjects compared to normosmic controls. Frasnelli *et al*. (2010) further found that acquired anosmics exhibit higher thresholds compared to congenital anosmic subjects, indicating that late onset has a greater negative impact on trigeminal chemosensation, perhaps due to failure of compensatory mechanisms in the adult. In the same vein, these authors had earlier failed to find differences in trigeminal sensitivity between groups of congenitally anosmic and normosmic control subjects, using the lateralisation method (Frasnelli *et al*., 2007b). Finally, only one research group has investigated discrimination and identification of bimodal trigeminal stimuli. Laska *et al*., (1997) found that despite their lack of olfactory perception, congenital anosmics can verbally describe bimodal odorants such as menthol, ethanol and cineole using similar adjectives compared to those used by normosmics. Furthermore, such patients can discriminate between bimodal odorants as well as normosmic controls do, albeit with slightly decreased performance due to the inability to smell.

4.2.2. Imaging Studies

Brain imaging studies investigating the effects of the absence of smell perception on trigeminal processing, point towards a general reduced recruitment of trigeminal areas in anosmic subjects. Electrophysiological studies measuring trigeminal event-related potentials (tERPs) and negative mucosal potentials (NMPs) give insight into central and peripheral trigeminal processes, respectively. For example, Frasnelli *et al*. (2007b) found that congenital anosmics displayed a higher peripheral response (higher NMP amplitudes) combined with a similar central activation (equivalent tERP latencies and amplitudes) compared to normosmic control subjects. However, acquired anosmic patients exhibited increased tERP latencies and reduced tERP amplitudes compared to healthy normosmic participants (Ren *et al*., 2012; Yang *et al*., 2012). Furthermore, using fMRI, Iannilli *et al*., 2007 found weaker activations in trigeminal processing areas, such as the right somatosensory cortex and left parietal insula, following pure trigeminal stimulation with CO_2 in a mixed group of congenital and acquired anosmic subjects compared to normosmic control subjects. Similarly, by stimulating the participant's nose with a bimodal odorant such as menthol or eucalyptol, our group and others have found reduced activations in trigeminal and olfactory cortical areas in congenital

(Gagnon *et al*., 2012) or acquired (Henkin *et al*., 2002; Iannilli *et al*., 2011) anosmic subjects compared to normosmic controls.

Consideration of these results lead Frasnelli *et al*. (2007b, 2011) to suggest a model of mixed sensory adaptation/compensation whereby the peripheral trigeminal response is inhibited by intrabulbar trigeminal collaterals in normosmia, thereby causing a functional downregulation of responsiveness to odorants in the periphery. When a healthy subject smells a bimodal olfactory odorant, his/her central trigeminal response is potentiated by olfactory co-stimulation. In anosmia, however, peripheral inhibition is released, allowing increased peripheral susceptibility, together with a reduced central (bimodal) response.

4.3. Summary

Studies of congenital and acquired anosmia in humans indicate that when one chemical sense such as olfaction is absent since birth, individuals experience reduced gustatory and/or trigeminal perceptions compared to normosmic subjects. Functional imaging studies furthermore demonstrate that the flavour network becomes functionally impaired, resulting in attenuated brain activation in response to chemicals perceived either outside (i.e. orthonasal bimodal odorant) or inside (i.e. taste) the body. These findings demonstrate how the chemical senses complement each other to give rise to a unified percept that characterizes chemical objects and information in the exterior and interior worlds (Stevenson *et al*., 2014a, b).

5. Conclusion

Whereas vision in many mammalian and avian lineages has developed at the expenses of orthonasal olfaction, vision remains essential and complementary to taste perception in humans. Loss of vision early in life gives scope to retrain the chemical senses, so as obtain improved exteroceptive functions. This allows the blind to have enhanced orthonasal olfactory sensitivity that is facilitated by the recruitment or invasion of disused cortical territory. In contrast, the blind have lower sensitivity for chemical senses responsive to interoceptive stimuli, i.e. retronasal olfaction and taste, and do not recruit additional occipital cortex. Moreover, loss of the sense of smell does not vacate significant amounts of cerebral cortex for use by other modalities, and is associated with reduced chemosensory sensitivity. In this

situation, the flavour network exhibits lower activations to tastes and trigeminal odours. We suggest that unlike anosmics, the congenitally blind are able to retrain their exteroceptive chemical senses and recruit additional cortical areas to improve their processing of chemical information arising in the surrounding environment.

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Discussion générale

Les résultats confirment la majorité des hypothèses de départ. Le premier article a démontré qu'effectivement, les aveugles congénitaux détectent et identifient moins bien les goûts de base que les sujets voyants aux yeux bandés. Ceci contraste grandement avec leurs habiletés à toucher, sentir (via la voie orthonasale) et écouter qui sont souvent améliorées par rapport aux voyants (revue dans Kupers & Ptito, 2014). De plus, les questionnaires indiquent que malgré leur manque de vision et les obstacles reliés à la recherche et la préparation de nourritures, les aveugles congénitaux ne sont pas plus néophobiques que les voyants et sont même réceptifs à varier leur diète et essayer de nouveaux plats, ce qui infirme nos hypothèses quant à leurs habitudes alimentaires. Le deuxième article a confirmé que les habiletés olfactives des aveugles dépendent grandement de la voie de stimulation. Alors que les aveugles identifient plus rapidement et tendent à mieux performer lorsqu'ils sentent les parfums de nourriture via leurs narines (voie orthonasale), ils tendent aussi à faire plus d'erreurs d'identification que les voyants lorsque les stimuli odorants sont placés sur la langue et sentis via le nasopharynx (voie rétronasale). Le troisième article a confirmé par IRMf que les aveugles activent plus faiblement leur cortex gustatif primaire et leur hypothalamus par rapport aux voyants lorsqu'ils goûtent. Fait intéressant, les aveugles ne recrutent pas leur cortex occipital pour goûter, un résultat pointant vers l'absence de plasticité intermodale pour la gustation chez l'aveugle congénital.

Le quatrième article a démontré que les handicapés olfactifs congénitaux identifient moins bien le goût amer et activent plus faiblement leur cortex gustatif (cortex orbitofrontal médial) durant cette tâche par rapport aux sujets contrôles normosmiques. De plus, la force de ces activations est directement proportionnelle à leurs habiletés à sentir et détecter une odeur. Enfin, le cinquième article propose que la plasticité des sens chimiques diverge chez l'aveugle et l'anosmique congénitaux de sorte que les aveugles :

1. sont capables d'entrainer leurs sens extéroceptifs (ex : olfaction orthonasale, toucher) et d'améliorer leurs performances par rapport à celles des voyants afin de compenser leur perte de vision
2. recrutent leur cortex occipital pour traiter les stimuli extéroceptifs

3. performent (ou tendent à performer) moins bien que les voyants dans le traitement de stimuli intéroceptifs (goûts, odeurs rétronasales)
4. et ne recrutent pas leur cortex occipital pour traiter les stimuli intéroceptifs.

Ceci contraste avec les handicapés olfactifs congénitaux qui ne possèdent pas suffisamment de cortex « olfactif » libre pour permettre la plasticité intermodale. Ainsi, les anosmiques performent moins bien dans des tâches chimiosensorielles et activent plus faiblement leur circuit responsable du traitement des saveurs lorsqu'ils goûtent ou sentent des odeurs à caractère trigéminal.

1. Explications des résultats comportementaux chez l'aveugle

Deux principaux arguments permettent d'expliquer les résultats obtenus chez les aveugles. Le premier suggère que la plasticité est induite par l'expérience alors que le deuxième repose sur la complémentarité des portées perceptuelles de la vision et du goût.

1.1 Plasticité induite par l'expérience

Telle que présentée dans l'introduction, la diète des aveugles semble souffrir de variété par rapport à celle des voyants (Bilyk *et al*., 2009). Ceci sous-expose la langue des aveugles aux stimuli gustatifs et entraîne des performances gustatives plus faibles. Plusieurs travaux soutiennent cette notion de plasticité induite par l'expérience, non seulement dans le système gustatif mais dans tout système sensoriel. Tel que discuté dans l'article 1, la majorité des performances auditives, tactiles et olfactives améliorées des aveugles sont restreintes aux tâches dans lesquelles ils s'entraînent davantage par rapport aux voyants. Par exemples, leur habileté à discriminer des stimuli tactiles avec les doigts est améliorée chez les lecteurs de Braille (Alary *et al.*, 2009, Wong *et al*., 2011) tandis que leur performance à discriminer les hauteurs sonores pourrait s'expliquer par leur entraînement en écholocation (Kellog, 1962; Teng *et al*., 2012), un comportement qui repose sur cette habileté (Schenkman & Nilsson, 2011). Tout comme ces modalités, la plasticité du système gustatif repose grandement sur l'expérience mesurée par la diète, tel qu'élégamment démontré par Kobayashi et collègues (2002; 2006).

Pour tester si la diète des aveugles corrèle avec leurs performances gustatives inférieures, il faudrait trouver une façon de quantifier la prise de nourriture dans la semaine précédant la mesure des seuils. Jusqu'à présent, les outils d'évaluation diététique sont des *Food Frequency Questionnaires* (FFQ) qui questionnent la fréquence de consommation de nourritures typiquement retrouvées dans les supermarchés. Ces FFQ varient en fonction des régions du monde puisqu'ils sont adaptés à chaque culture. Les nourritures consommées sont ensuite décomposées en nutriments, ce qui permet de mesurer l'apport nutritionnel hebdomadaire en glucides, lipides, protéines, etc. Cependant, ils ne renseignent pas sur l'expérience gustative elle-même puisque ces nutriments ne peuvent pas être associés à des goûts spécifiques. La solution serait donc de construire et valider un FFQ ciblant les nourritures contenant les composés chimiques caractéristiques des goûts sucré, salé, acide, amère et umami et ainsi mesuré la quantité de stimuli gustatifs auquel est exposé le participant. Il n'existe encore aucun outil validé de ce type et plus de travaux seront nécessaires afin de répondre à cette question.

1.2 Portées perceptuelles complémentaires de la vision et du goût

Un second argument permettant d'expliquer les résultats comportementaux observés chez les aveugles concerne la portée perceptuelle des sens étudiés. Cette dernière désigne la distance à laquelle l'organisme peut percevoir un stimulus. Par exemple, grâce à son œil aiguisé, un chasseur d'orignal est capable de localiser sa proie située entre lui et, ultimement, l'horizon. À mesure qu'il s'en approche, il vient à graduellement apprécier ses meuglements, son parfum musqué et – si la chasse s'avère profitable - la chaleur de son corps et la texture de son pelage. Tous ces stimuli peuvent être perçus en supplément des impressions visuelles, puisque la portée perceptuelle de la vision chevauche celle de l'audition, de l'odorat (voie orthonasale) et du toucher (Figure 4C). Ce n'est que lorsque le chasseur s'assoit à table pour déguster sa prise que les saveurs boisées de la viande et les sensations d'assouvissement qui en résultent ne peuvent être perçues simultanément par le regard. Ainsi, les portées perceptuelles de la vision et du goût ne se chevauchent pratiquement jamais. Elles se complètent de sorte que l'une précède l'autre durant la consommation et devient un complément grâce auquel l'expérience alimentaire est mise en contexte.

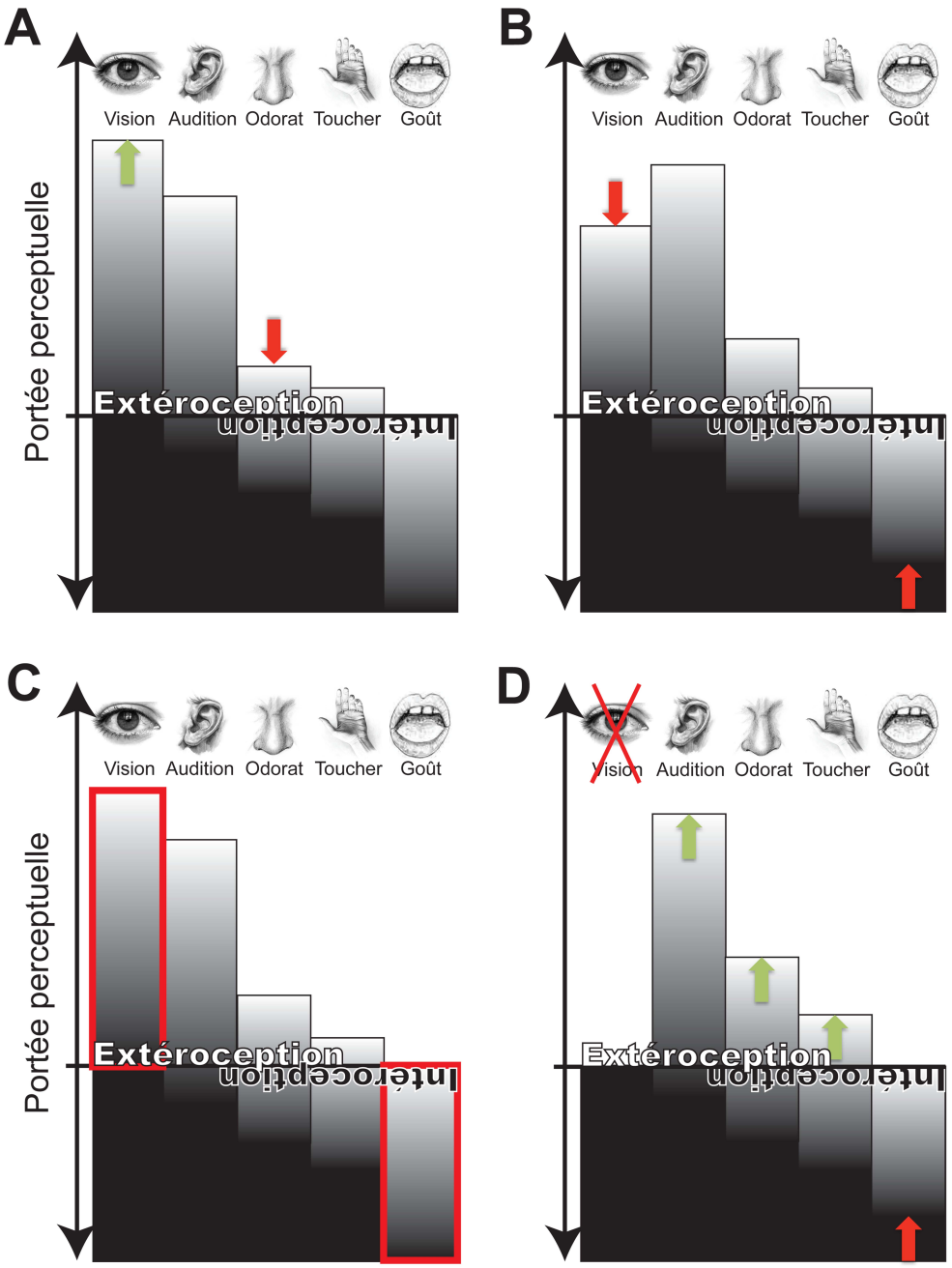

Figure 4. Compromis sensoriels évolutionnaires: le perfectionnement de la vue est associé à la diminution de l'odorat (**A**) tandis que la diminution de la vue concorde avec la diminution du goût (**B**). Les portées perceptuelles extéroceptive de la vision et intéroceptive du goût ne se chevauchent pas, mais sont séquentielles et complémentaires (**C**). Chez l'aveugle congénital, la perte de vision est associée au perfectionnement des sens extéroceptifs mais aussi à la diminution du sens intéroceptif (**D**). Les flèches rouges et vertes indiquent respectivement une diminution et une amélioration. Le toucher inclut les thermoception, somatosensation, nociception, chémosensation trigéminale et proprioception.

Hors, les études évolutionnistes présentées dans l'article 5 (Gagnon *et al*., 2014b) semblent indiquer que le perfectionnement des sens survient parfois au détriment de d'autres, à condition que leur portée perceptuelle se chevauche. Ainsi, les sens pourraient se faire concurrence dans l'accomplissement d'une même fonction et la sélection du vainqueur dépendrait de la grandeur de sa portée perceptuelle. Par exemple, lorsque les grands singes mâles ont acquis une vision trichromatique comme celle des femelles possiblement afin de raffiner leur recherche de nourriture et leurs interactions sociales elles-mêmes médiées par l'odorat, cet accroissement fonctionnel visuel a coïncidé avec une détérioration olfactive mesurée par une proportion grandissante de pseudogènes (Gilad *et al*., 2004). Ainsi, alors que la vision bénéficie d'une amélioration, les habiletés olfactives déclinent (Figure 4A). À l'inverse, quand les portées perceptuelles de deux sens ne se chevauchent pas, la diminution de performance de l'un semble être associée au déclin de l'autre, du moins chez les espèces vivant dans un environnement aérien (Figure 4B; Gagnon *et al.*, 2014b; Jones *et al*., 2013).

Dans le cas des aveugles congénitaux, le manque du sens exclusivement extéroceptif a pour effet de maximiser les autres sens qui miment ses fonctions, à savoir l'audition, l'olfaction orthonasale et le toucher (Figure 4D). Cette compensation sensorielle permet à l'individu de maximiser la connaissance de son environnement extérieur. Cependant, comme les portées perceptuelles de la vision et du goût ne se chevauchent pas, il n'est pas utile pour l'aveugle de compenser sa perte de vision par une amélioration de la gustation. Comme les portées perceptuelles sont complémentaires et séquentielles lors de la prise alimentaire, la perte de la vision entraîne une diminution du goût (Figure 4D) et une tendance semblable est observée pour l'olfaction rétronasale.

Le goût n'est pas le seul sens exclusivement intéroceptif. Selon Craig (2003), la nociception l'est aussi et pourtant, des études dans notre laboratoire (Slimani *et al*., 2013; 2014) ont démontré que les aveugles bénéficient d'une hypersensibilité à la douleur, soit une amélioration de leur nociception. Comment alors expliquer que deux sens intéroceptifs tels que le goût et la nociception soient diminué pour l'un et augmenté pour l'autre chez l'aveugle congénital? Une explication possible repose sur la séquence d'utilisation des sens qui diverge en fonction du comportement. Lors de la prise alimentaire, l'individu regarde d'abord sa nourriture avant d'y goûter. À l'inverse, lorsque quelqu'un se blesse, l'individu se fait d'abord mal - sans nécessairement voir la source nociceptive - puis utilise sa vision pour vérifier

l'étendue des dommages, une réponse aux pouvoirs analgésiques (Longo *et al*., 2009). La deuxième explication repose sur le débat du caractère intéroceptif de la douleur. Dans leur expérience, Slimani et collègues (2013, 2014) ont utilisé des sources extérieures de chaleur et de froid pour stimuler la peau des participants. Bien qu'elles renseignent sur l'état physiologique du corps, ces perceptions thermales et nociceptives peuvent aussi être perçues comme étant extéroceptives puisqu'elles sont attribuées à des objets extérieurs au corps et/ou en contact avec la peau (Haggard *et al*., 2013).

2. Explications des résultats d'imagerie

2.1. Absence de plasticité intermodale en gustation chez l'aveugle

L'un des autres résultats intéressants de cette thèse est l'indication d'absence de plasticité intermodale en gustation chez l'aveugle congénital. La plasticité intermodale chez l'aveugle est maintenant expliquée par un nombre grandissant d'études pointant vers l'hypothèse de *constance fonctionnelle* (Fine, 2014). Par exemples, l'exploration ou l'interaction avec le monde extérieur, notamment via l'utilisation de substitution visuotactile (ex : TDU) ou visuoauditive (ex : vOICe), permet aux aveugles de recruter les aires normalement « visuelles » dédiées au traitement du mouvement (aire V5/hMT+; Matteau *et al*., 2010), de formes bi- et tridimensionnelles (aire latérale occipitale visuotactile ou LOtv; Amedi *et al*., 2010; Merabet *et al*., 2009; Ptito *et al*., 2012), de mots (aire visuelle des mots; Striem-Amit *et al*., 2012), de visages (aire fusiforme des visages ou FFA; Goyal *et al*., 2006), de corps en mouvement (aire extra-striée du corps ou EBA; Striem-Amit & Amedi, 2014) ou de routes (parahippocampe; Kupers *et al*., 2010). Ensemble, ces études indiquent que lorsqu'un individu aveugle ou voyant perçoit un stimulus afin de l'identifier, le situer ou interagir avec lui, il recrute les voies neuroanatomiques fonctionnelles dédiées à l'analyse du « Quoi? » (voie ventrale) et du « Où?/Comment? » (voie dorsale) caractéristiques du système visuel (Bonino *et al*., 2008; Fiehler & Rosler, 2010; Ptito *et al*., 2009; 2012).

Or, l'information chimique gustative ne renseigne que très peu sur l'identité d'une nourriture. Les goûts sucré, salé, acide, amer ou umami sont communs à une très grande variété de plats et de breuvages et leur identification est normalement effectuée avant la mise en bouche. De plus, ce n'est pas tant les sensations gustatives qui permettent de situer un

aliment mais plutôt la somatosensation. Contrairement à l'odorat qui peut, jusqu'à un certain point, se diviser en voies « ventrale » et « dorsale » analogues au système visuel (Clarke & Tyler, 2014; Frasnelli *et al*., 2012; Koster *et al*., 2014), l'organisation anatomofonctionnelle de la gustation est très peu semblable à celle de la vision. Par exemples, en plus des voies hédoniques et sensorielles spécialisées dans l'analyse du plaisir et de l'intensité des goûts (Sewards, 2004), les travaux de Cauda *et al*. (2011) ont démontré deux circuits fonctionnels partant de l'insula: un premier antérieur impliqué dans l'intéroception, les émotions et l'attention et le deuxième postérieur contrôlant l'orientation squélétomotrice du corps et la sélection de réponse(s). De plus, l'insula a récemment été proposée comme le substrat anatomique de la mémoire de reconnaissance des objets et des goûts (Bermudez-Rattoni, 2014), impliqué dans la transition de la nouveauté vers la familiarité, transition d'autant plus efficace si l'expérience est associée à du stress ou des émotions fortes recrutant l'amygdale (ex : guerre, Wansink *et al*., 2009; solitude, Troisi *et al*., 2011). Finalement, à la lumière du rôle du système gustatif dans la perception temporelle (Parent *et al*., 2014; Tomasi *et al*., 2014), la motivation et la prise de décision (Parent *et al*., 2014; Naqvi & Bechara, 2010), il semblerait plutôt que la gustation et l'intéroception se spécialisent dans l'analyse de différentes questions, telles que « Quand? » et « Pourquoi? ».

2.2. Absence de plasticité intermodale en gustation chez l'anosmique

Contrairement aux fonctions du système visuel qui diffèrent de celles de la gustation, celles de l'olfaction parviennent à les reproduire. Par exemples, les odeurs évoquent des souvenirs clairs (Koster *et al*., 2014) et leur évaluation hédonique motive différents comportements humains (Cabanac, 1971; Kringelbach, 2004). L'absence de plasticité intermodale en gustation chez l'anosmique ne peut donc pas s'expliquer par l'hypothèse de la constance fonctionnelle de Fine (2014). Chez l'aveugle et le sourd de naissance, deux hypothèses structurelles ont été suggérées pour justifier la plasticité intermodale. La première propose que le recrutement d'un cortex sensoriel privé de stimulations par un autre sens est permis par le démasquage ou le renforcement de connexions cortico-corticales (pré)existantes, alors que la deuxième l'explique par le recâblage via de nouvelles connexions thalamo-corticales (Desgent & Ptito, 2012). Bien qu'une étude de cas chez l'Homme pointe vers le renforcement de connexions cortico-corticales (Ioannides *et al*., 2013), une variété d'études

animales soutiennent l'hypothèse du recâblage via le thalamus (revue dans Horng & Sur, 2006). Si la plasticité intermodale dépend effectivement d'un recâblage via le thalamus, alors l'organisation anatomique du système olfactif pourrait expliquer l'absence de plasticité intermodale chez l'anosmique. Contrairement au système visuel dans lequel les afférences rétiniennes projettent vers les corps genouillés latéraux, le système olfactif possède une voie qui évite le relais thalamique permettant aux afférences bulbaires de faire directement synapse dans le cortex piriforme avant de projeter vers le cortex orbitofrontal (Tham *et al*., 2011). De plus, une récente étude chez le rat indique que l'organisation topographique du cortex olfactif primaire (piriforme) est indépendante de ses afférences sensorielles (Chen *et al*., 2014). Ceci contraste grandement avec les autres modalités comme la vision ou l'audition dont l'organisation topographique des cortex primaires dépend des intrants sensorielles (Casagrande & Kaas, 1994; Formisano *et al*., 2003). Au contraire, l'organisation du cortex piriforme s'apparente davantage à celle d'un cortex intégratif alors que le bulbe olfactif représenterait l'équivalent d'un cortex sensoriel primaire (Johnson *et al*., 2000). Considérant l'isolement périphérique du bulbe et l'organisation anatomique du système olfactif, il est probable que les deux hypothèses structurelles sous-tendant la plasticité intermodale expliquent son absence chez l'anosmique congénital.

3. Implications cliniques

Puisque le sens du goût subit des changements plastiques importants suivant l'expérience, ceci suggère que l'apprentissage de la cuisine et de la gastronomie et la modification de la diète pourraient perfectionner ce sens chez les personnes ayant une basse vision ou des troubles olfactifs. De plus, compte tenu des liens étroits entre les troubles gustatifs et la dépression et l'anxiété (Amsterdam *et al*., 1987; Heath *et al*., 2006) ainsi que le rôle de la nourriture dans la synchronisation des cycles circadiens (Tanaka *et al*., 1999), l'entraînement gustatif via des cours de cuisine et une alimentation variée suggère que la santé psychologique et la qualité du sommeil, toutes deux fortement affectées chez les handicapés visuels (Agrawal & Kaur, 1985; Bolat *et al*., 2011; Huurre & Aro, 1998; Jones *et al*., 2009; Okawa *et al*., 1987; Tabandeh *et al*., 1998), pourraient en bénéficier. Par exemple, le caractère convivial des repas encourage le sentiment d'appartenance à un groupe, ce qui permet de

contrer l'isolement. De plus, la cuisine permet de découvrir des saveurs du monde et offre une manière de voyager très abordable. La préparation de repas peut aussi représenter une forme d'expression pouvant contribuer à la réalisation de soi. D'ailleurs, les cours de cuisine ont été suggérés par un certain psychologue, Dr. Mark Salter, comme remède pour contrer la dépression (Fleming, 2014). Bien que cette activité présente plusieurs obstacles pour les non-voyants, le défi de cuisiner comme d'y prendre plaisir n'est pas impossible. À cet effet, la performance impressionante de la jeune chef Christine Ha, aveugle tardive et gagnante de la série de téléréalité culinaire MasterChef (mettant en scène Gordon Ramsay ainsi que des candidats voyants, diffusée sur le canal FOX), prouve que le défi peut se relever haut la main. Il reste maintenant à transmettre des conseils et méthodes adéquats pour encourager les non-voyants à apprivoiser l'environnement hostile que représente souvent la cuisine.

4. Le goût : un système perceptuel

Finalement, les résultats chez l'aveugle congénital indiquent que bénéficier de la vision avantage le goût. Ceux-ci rejoignent les points de vue de Gibson (1966) et d'Auvray & Spence (2008) qui remettent en question la taxonomie des sens. Selon eux, la gustation ne devrait pas être considérée comme une modalité sensorielle simplement chimique mais plutôt comme une modalité *perceptuelle* orientée vers l'objet. Selon ce point de vue, la perception unifiée de goûts ou de saveurs inclut non seulement le goût, l'odorat, la somatosensation et le sens trigéminal mais aussi la vision et l'audition. Ces perceptions unimodales se fusionnent ensemble au cours de la prise alimentaire puisqu'elles sont attribuées à une même nourriture.

De plus, à la lumière d'une variété de travaux en neuroesthétique (Brown *et al*., 2011; Chatterjee *et al*., 2009; Ishizu & Zeki, 2011, 2013; Jacobsen *et al*., 2006; Kawabata & Zeki, 2004; Tsukiura & Cabeza, 2011), savourer ou goûter ne se limiterait pas à de simples sensations chimiques ou intéroceptives. Goûter inclurait d'abord et avant tout une évaluation de la valence de l'objet (ex : attractif vs répulsif) dans le but de satisfaire un besoin. Par exemple, en analysant près d'une centaine d'études en neuroimagerie, Brown et collaborateurs (2011) ont démontré que l'évaluation de la beauté active les cortex gustatifs primaires (insula antérieure) et secondaires (cortex orbitofrontal) peu importe la modalité sensorielle impliquée

pour le percevoir. Selon leurs résultats, l'insula antérieure et le cortex orbitofrontal représenteraient une aire amodale de convergence pour le premier et une aire supramodale de contigüité pour le second, recrutées durant une évaluation esthétique à travers la gustation, l'olfaction, la vision ou l'audition. Cette évaluation concerne non seulement la nourriture mais également tous les stimuli pouvant satisfaire les besoins de l'Homme, à savoir les besoins homéostatiques (ex : chaleur), sexuels (ex : reproduction), sociaux (ex : appartenance à un groupe) et sociétaires (ex : contemplation d'œuvres artistiques).

C'est donc l'interaction dite « alliesthésique » (Cabanac, 1971) entre un sens extéroceptif comme la vision (ex : vue d'une pomme rouge) et l'intéroception (ex : faim) qui stimule en premier lieu le système gustatif et permet l'évaluation de la valence d'un fruit comme d'une œuvre d'art. Suivant l'expérience (ex : consommation), cette évaluation évolue ensuite en une évaluation de la valeur (ex : bon vs mauvais) qui cultive et affine le goût. Lorsque considéré comme une modalité perceptuelle, le goût aurait donc pour fonction principale de permettre la transformation de l'organisme via l'attirance – souvent fusionnelle – et/ou le rejet d'objets et même de situations émanant de l'environnement extérieur. La polysémie de l'expression « avoir du goût », utilisée autant pour décrire un aliment savoureux qu'un esthète amoureux de la beauté, prendrait donc racine dans ses bases neurologiques.

Conclusion

En résumé, cette thèse a démontré que voir avantage le sens du goût. Alors que les aveugles de naissance peuvent améliorer leurs sens extéroceptifs pour comprendre le monde qui les entoure, goûter ne permet pas de compenser leur perte de vision. De plus, l'absence de plasticité intermodale en gustation chez l'aveugle suggère que le système gustatif remplisse d'autres fonctions que celles du système visuel. Les résultats chez l'anosmique confirment par ailleurs que sentir améliore le goût. L'absence de plasticité intermodale en gustation chez l'anosmique propose que l'organisation anatomique du système olfactif ne soit pas optimale pour permettre la plasticité intermodale. Compte tenue de la grande susceptibilité plastique du système gustatif face à l'expérience et l'entraînement, les travaux présentés ici encouragent fortement la société tout comme les professionnels de la réadaptation à améliorer l'accès à une alimentation variée, riche et adéquate chez les personnes privées d'un sens. Ceci est d'autant plus important puisque la relation avec la nourriture est un aspet crucial de la qualité de vie.

1. Pistes de recherche

Finalement, si l'impact de la cécité sur le sens chimique du goût est maintenant élucidé, alors il reste à découvrir l'impact de l'absence de vision sur le système perceptuel du goût, impliqué notamment dans le jugement esthétique. Puisque goûter implique la sélection préalable de nourritures, alors certaines questions demeurent : Qu'est-ce qui rend la nourriture attrayante chez les non-voyants? Quels sont leurs critères de beauté qui, par exemple, les aident à sélectionner des fruits et légumes? Ces critères sont-ils comparables à ceux des sujets voyants, lesquels sont fortement exposés aux idéaux de symétrie, respect des proportions et couleurs stéréotypes? Si ces critères sont différents, les personnes voyantes ne devraient-elles pas prendre exemple sur les perceptions des aveugles pour améliorer leurs choix de consommation?

Ces réponses sont d'autant plus importantes que le rôle de la vue dans l'alimentation génère plusieurs problématiques autant agroalimentaires, économiques, environnementales que éthiques. Par exemple, les fruits et légumes difformes sont laissés de côté et contribuent

au gaspillage alimentaire, maintenant estimé à près du tiers de la production mondiale (United Nations Environment Programme, 2013). De plus, l'industrie agroalimentaire investit massivement dans le développement d'espèces transgéniques qui satisfont les critères de beauté visuelle, souvent au détriment de leurs autres qualités sensorielles, nutritionnelles et même sanitaires (Bawa & Anilakumar, 2013).

Similairement, si le système gustatif permet, comme l'a suggéré Brown et collègues (2011), d'encoder toutes les formes de beauté qui nous entourent, alors quelle est la beauté aveugle? À quel point les non-voyants sont-ils sensibles aux critères de beauté visuelle? Ces critères les attirent-ils autant que les voyants? Pour reprendre l'idée de St-Exupéry (1943)[4], se pourrait-il que voir sans les yeux permette de mieux juger la valeur d'un objet?

Dans son magnifique éloge à la beauté parue dans le journal La Presse en janvier 2011, Isabelle Hachey rapportait à ce sujet le regard de ces personnes capables de « voir l'invisible ». L'un d'eux accusait d'ailleurs le monde actuel d'exercer un « oculocentrisme totalitaire », soit un régime si dominant qu'il contrôle les manières et habitudes intimes, i.e. l'apparence. La beauté chez les personnes aveugles est forcément perçue autrement. Elle réside par exemples dans « la voix assurée des gens beaux », le « son du sourire », la « douceur de la peau », la « chaleur du soleil qui caresse le visage », l' « odeur de la mer » (Hachey, 2011).

Dans une société rivée sur les écrans, qui valorise l'apparence et la définition du soi par l'extéroception (ex : égoportraits) plutôt que par l'intéroception (ex : introspection; Delisle, 2014), la vision serait-elle un handicap, i.e. un sens qui peine à distinguer la valeur morale du jugement esthétique (Durrigl, 2002; Griffin & Langlois, 2006; Tsukiura & Cabeza, 2011)? Tel que suggéré par Fine (2014), se pourrait-il que « les aveugles possèdent des représentations du monde sans équivalents chez les voyants »? Si c'est le cas, alors il est grand temps que les personnes voyantes s'inspirent de leurs confrères peut-être pas si aveugles qu'ils ne le laisseraient paraître.

[4] « On ne voit bien qu'avec le cœur. L'essentiel est invisible pour les yeux. », *Le Petit Prince*.

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