Quantitative EEG in Schizophrenia: Current State and Future Direction

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Summary

The research paradigm of biological psychiatry assumes that mental disorders can be explained by structural and functional changes in the brain. Indeed, schizophrenia patients show many biological abnormalities, including consistent EEG alterations. However, these findings are still insufficient for a clinical impact. One explanation for this gap is the heterogeneity of the disorder and the biological measurements, because, a) on the psychopathological level, widely different symptoms are summarized under the same diagnosis, and b) on a neurophysiological level, the EEG represents a mixture of brain processes that cannot easily be separated. The different EEG analysis strategies that have been used so far prove some sensitivity in finding biological abnormalities for schizophrenia. However, the models we use to decompose the mixture in the EEG have to be further elaborated, and need to be related to biologically informative definitions of the psychopathological state of patients.

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Key words: Inverse problems, modelling, psychopathological dimensions, heterogeneity

Quantitatives EEG bei Schizophrenie: Heutiger Stand und zukünftige Ausrichtung

Das Forschungsparadigma „biologische Psychiatrie“ geht davon aus, dass psychiatrische Erkrankungen durch Veränderungen in der strukturellen und funktionellen Hirnorganisation erklärt werden können. Schizophreniepatienten zeigen in der Tat eine Reihe biologischer Veränderungen, insbesondere auch EEG-Anomalitäten. Trotzdem sind diese Befunde in der Klinik wenig relevant. Eine mögliche Erklärung dafür stellt die Heterogenität der schizophrenen Erkrankung und der biologischen Daten dar, weil a) aus psychopathologischer Sichtweise dieselbe Diagnose sehr unterschiedliche Symptome beinhalten kann, und weil b) aus neurophysiologischer Perspektive das EEG aus vielen, gleichzeitig aktiven Hirnprozessen hervorgeht, welche schwierig voneinander zu trennen sind. Die verschiedenen bisher genutzten EEG-Analysemethoden können zwar biologische Veränderungen der Schizophrenie nachweisen, aber die Modelle zur Beschreibung des EEG als raumzeitliche Hirnprozesse müssen weiter verbessert und in Bezug gesetzt werden zu biologisch informativen Definitionen des psychopathologischen Status der Patienten.

Schlüsselwörter: Inverses Problem, Modellierung, psychopathologische Dimensionen, Heterogenität

EEG quantitatif dans la schizophrénie: état actuel et futures directions

Le paradigme de recherche de la psychiatrie biologique part du principe qu’un trouble mental peut être expliqué par des changements structuraux ou fonctionnels du cerveau. Les patients souffrant de schizophrénie présentent en effet de nombreuses anomalies biologiques, parmi lesquelles des modifications du tracé EEG. Cependant, ces modifications sont peu utilisées de routine en clinique. L’une des explications possibles est l’hétérogénéité des troubles cliniques ainsi que des données biologiques, puisque a) sur le plan psychopathologique, des troubles différents sont regroupés sous le même diagnostic, et b) sur le plan neurophysiologique, l’EEG résulte de nombreux processus cérébraux qu’il n’est pas aisé de séparer. Les différentes approches utilisées dans l’analyse de l’EEG ont démontré une certaine sensibilité dans la détection d’anomalies biologiques spécifiques pour la schizophrénie. Cependant, les modèles utilisés dans l’interprétation de l’EEG doivent encore être améliorés, et doivent être confrontés aux définitions biologiquement informatives sur l’état psychopathologique des patients.

Mots clés : Problème inverse, modélisation, dimensions de psychopathologie, hétérogénéité

Introduction

Biological psychiatry is a research paradigm that assumes that the causes of mental disorders can ultimately be explained by alterations in the structure and function of the brain. While there seems to be a broad consensus that there are no reasonable alternatives to this view, the promise of the paradigm, namely that the diagnosis and treatment of mental disorders receives its justification in fully biological terms, and that such a biological understanding of these disorders overcomes the current shortcomings of psychiatric diagnoses and treatments, seems yet to be unfulfilled.

An obvious explanation for this state of affairs can be given by referring to the immense complexity of the human brain in conjunction with the strong limitations of the historically and currently available methodology to assess human brain structure and function. But how far have we gotten, how useful are the existing findings today, and what may be the most reasonable next steps in this endeavor? The aim of the current article is to shed some light on these questions from the perspective of one of the oldest methods available to study an intact human brain "at work", namely the EEG, in one of the most severe mental disorders, namely schizophrenia. We will further limit the focus of this article on baseline EEG, because a) the plethora of tasks and the associated event-related potential (ERP) components that have been studied in schizophrenia cannot reasonably be accommodated within a single article, and because b) the brain's responses to any task demand do not occur in a void, but interact with the current baseline state of the brain. Alterations of baseline state are thus important candidates to causally explain alterations in task response because they precede in time, and thus potentially can modify task response.

Early visual characterization of EEG in psychiatry and pathological EEG findings

It is notable that the feasibility of EEG recordings in humans was the achievement of a psychiatrist. Hans Berger was driven by his hope for obtaining "a mirror into the brain" of his patients. Nevertheless, the primary impact of the availability of EEG measurements was in neurology, where particular, visually recognizable EEG patterns became pathognomonic for particular forms of neurological diseases, most importantly epilepsy. While there are still no pathognomonic EEG patterns of schizophrenia, there are nevertheless some important points to retain here:

- There seems to be an unspecific increase of abnormalities in the EEG of schizophrenia patients. In an overview that was assembled before quantitative EEG became the mainstream approach to EEG in schizophrenia, Itil [1] concluded that the rate of EEG abnormalities was higher in patients with schizophrenia compared to controls, and that these abnormalities were predominantly spikes and atypical sharp waves.
- Epileptic seizures may be followed by psychosis. In a recent review, Trimble and Kanner [2] concluded that up the 18% of patients that have intractable focal epilepsy may develop a postictal psychosis, but that the link between the seizures and the psychosis is often overseen because there is a characteristic delay between the seizures and the onset of the psychotic symptoms.
- Similarly, epilepsy seems to be a risk factor for psychosis. A recent systematic meta-analysis found that compared to controls, patients with epilepsy had an almost 8 times increased risk of also having a psychotic illness [3].

Quantitative spectral EEG (QEEG) for diagnosis and treatment prediction in schizophrenia

With the advent of the computational facilities to digitally record and process EEG data on a large scale, systematic efforts were made to find biomarkers of schizophrenia in quantitative spectral EEG [e.g. 1]. Already the first findings reported an increase of slow (theta and delta) power, other studies [e.g. 4] reported also a reduction of alpha-band power and increased high frequency (beta & gamma) activity. From early on, it has been argued that these effects were unlikely to be explained by medication, because they were stronger in unmedicated patients [5]. Meanwhile, the finding of increased slow wave activity has been confirmed in a meta-analysis [5], but the authors also noted that the effect sizes were moderate. Furthermore, the same group of authors concluded that there is a notable lack of effort towards using quantitative EEG as a clinical test for schizophrenia [6].

The attempts to use QEEG as a diagnostic tool for schizophrenia were complemented by efforts to characterize the EEG spectral signatures of psychoactive substances and thus obtain QEEG profiles of particular neurotransmitter systems [7]. On one side, the QEEG correlates of experimentally induced transient states of psychosis were investigated [e.g. 8 (Amphetamine), 9 (Ketamine), 10 (Ayahuasca)]. On the other side, substances known to have a therapeutic effect upon existing psychotic symptoms were systematically studied [e.g. 4, 11] with the idea to identify a "key-lock" principle. This principle assumes that a drug with a QEEG profile opposite to the abnormalities observed in a patient would also counteract the symptoms observed in the patient. This view was in part motivated by the report that the abnormalities of QEEG of schizophrenic patients would aggregate in several clusters, but that these clusters would not systematically relate to the observed psychopathology [12]. Thus, it was concluded that there may be a series of biologically rather than

clinically defined subtypes of schizophrenia that may also have different treatment needs. However, the initial hope to predict treatment response based on the combination of QEEG profiles of individual patients and particular drugs has not been fulfilled [13].

Dealing with heterogeneity

The obvious explanation for the gap between the conviction that schizophrenia has a specific biological origin, and our capacity to explain schizophrenia in biological terms is that there is heterogeneity. Something like a mean EEG spectrum, which results from a large variety of processes, in a group of subjects commonly diagnosed with schizophrenia, but showing different symptoms, may not be sufficiently informative. Importantly, heterogeneity may blur the biological image both on the psychopathological and the neurobiological level:

- On the psychopathological level, two patients may have received the same diagnosis of schizophrenia, but have little to no overlap in the individual symptoms that lead to the diagnosis. It may therefore be quite unjustified to expect finding common markers of an underlying individual biological pathophysiology [14]. In addition, complex behavior is typically explained by the activity of large scale, and distributed cognitive networks. Thus, a symptom, as it appears on the behavioral level, may result from the interaction of several, potentially differentially altered functional entities, and/or from a disintegration of the networks themselves. This entails a non-trivial, and non-unique problem of defining the "right" psychopathological system. The problem has been increasingly recognized, and met by the development of various diagnostic systems that assess psychopathology in terms that may reasonably be related to putative brain functional and structural entities [15, 16].
- On the neurophysiological level, it is equally well known that the EEG signal, at the level of any single electrode, is produced by a mixture of brain processes that are separated in space, time, spectral distribution, and thus function. This implies that also EEG data needs to be "properly" unmixed to obtain biological indices that are specific for particular functions [17]. Scalp mapping of spectral power as function of frequency band may only be a first, but insufficient step to separate different indices of brain function. Similar problems arise for other neurobiological measurements.

To link psychopathology and EEG, both the psychopathological and the biological levels of the problem thus require a separation into the "right" entities. Unfortunately, these types of "unmixing" problems cannot be solved without a priori choices from the investigators. This entails that the choices that the investigators have to make are not easily justifiable post-hoc by the data; this would lead into circular arguments. The endeavor to understand "schizophrenia" in biological terms thus seems to be bound to a time-consuming, and iterative adaptation [18] of psychopathological and neurobiological models that take into account both phenomenological and theoretical considerations.

In the following section, we will briefly review a series of particular EEG models that have been applied to data from patients with schizophrenia. We will however not further develop the part about psychopathological models of schizophrenia, since this is a) not the scope of this journal, and b) not our expertise.

Models of EEG

Inverse models

One obvious strategy to further decompose EEG signals is through modeling the data in three-dimensional brain space, because different brain regions obviously implement different, and well-known brain functions. For resting state EEG, such so-called inverse models typically try to account for a potentially broadly distributed pattern of activity, and introduce a priori assumptions about this distribution. The probably most widely used type of assumptions is that there is a certain amount of spatial smoothness in brain electric activity, i.e. neighboring regions can be expected to show similar amounts of activation [19]. The so called LORETA (low resolution electromagnetic tomography) inverse solutions have repeatedly been applied to frequency transformed EEG data of patients with schizophrenia (**Figure 1**), and localized the previously reported slow wave abnormalities primarily to the frontal cortex [20 - 23] and temporal regions that have long been suspected to be abnormal in schizophrenia [24].

Microstate models

Schizophrenia has often been claimed to resemble a disconnection syndrome [25]. At the same time, in EEG data, it has often been noted that there is a remarkable amount of organization in patterns and dynamics of the recorded scalp electric fields. In particular, it has been observed that spontaneous EEG scalp electric fields display quasi-stable configurations for periods of approximately 80 msec on average, before rapidly changing into a new configuration that again persists for a certain period of time (**Figure 2**). These quasi-stable periods have been called microstates [26]. Conceptually, it can be argued that microstates must have been generated by a network of brain regions that operate in a synchronous, non-lagged mode [27], which dovetails with theoretical considerations about puta-

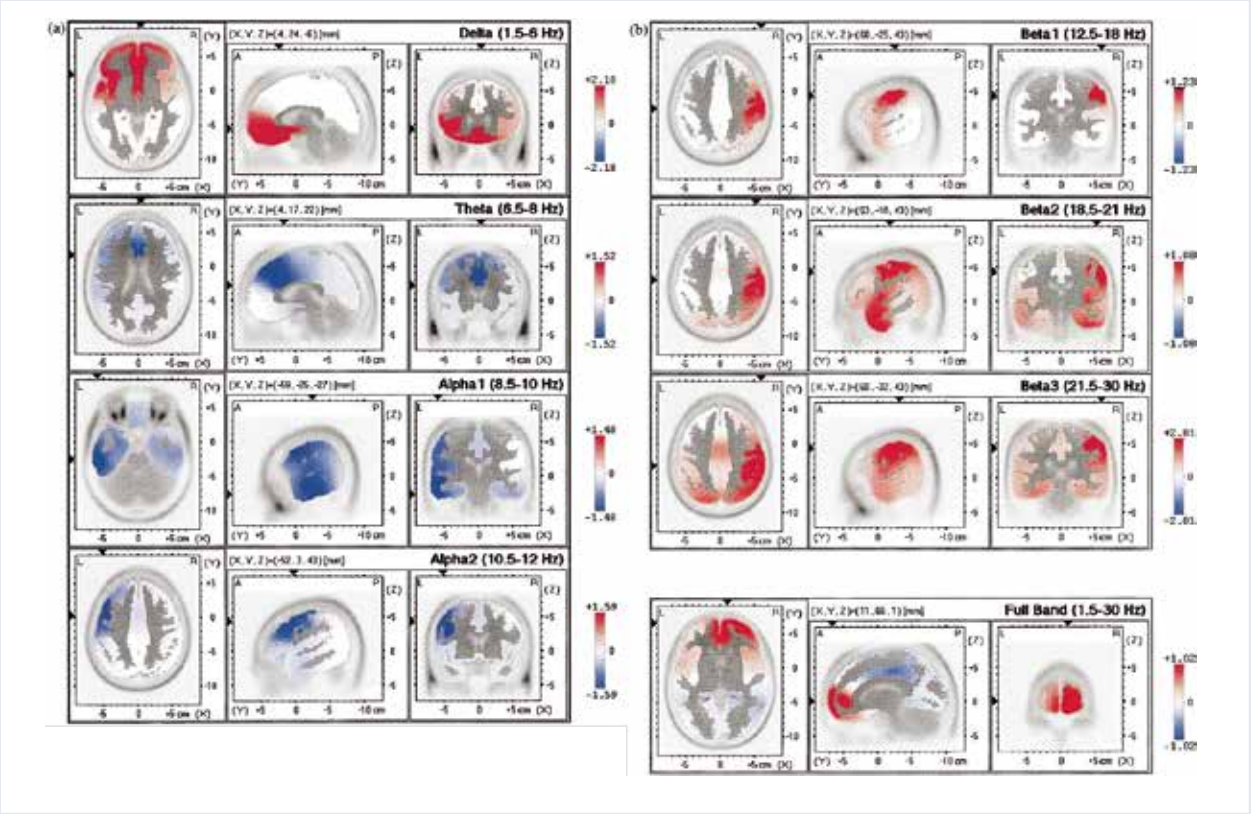

Figure 1: Images of voxel-by-voxel t-statistics of brain regional electrical activity using LORETA, for the 7 frequency bands and the "full band", and comparing 9 acute, medication-naive schizophrenic patients vs. 36 control subjects; hyperactivity (excess) in patients is indicated by red, hypoactivity (deficit) by blue. From Pascual-Marqui, Lehmann [22], with permission.

tive non-causal binding mechanisms in brain networks [28]. Furthermore, the spatial configurations of these microstates cluster well into a small set of prototypical configurations [26, 29, 30]; an observation that anticipated similar conclusions coming from fMRI data [31], however, without directly giving information about the involved regions. Later studies combining EEG and fMRI have shown that there is indeed a systematic relationship between EEG microstates and fMRI resting state networks [32].

Schizophrenia patients have been shown to have systematic abnormalities in microstate parameters. A recent meta-analysis by Rieger, Diaz Hernandez [33] concluded that a particular class of microstates related to a fronto-parietal executive control network was impaired in patients, whereas a microstate class related to saliency processing was over-active. The effect sizes were higher than those found in classical spectral analyses [5], but lower than in evoked potential studies. Furthermore, some of these microstate parameters were found to be related to the presence of auditory verbal hallucinations, and to treatment response. Diaz Hernandez and Rieger [34] have recently also been able to show that such microstate features can be systematically modified using a neurofeedback training protocol, which may offer new treatment options in the future.

Future directions

The fact that there are consistent, but not sufficiently well defined EEG abnormalities in what is called schizophrenia, and the fact that several, conceptually very different analysis strategies such as spectral analysis and microstates prove to be sensitive for schizophrenia indicates that the models we employ to decompose the EEG before it can be related to the psychopathological state of a patient are only partially suited, and need to be elaborated further. In particular, it seems to be necessary to apply methods that simultaneously do justice to the frequency domain information, to the network features of the signal and to the transient dynamics of the signal. The complex patterns of correlation of fMRI networks with EEG spectra [35] and the role of EEG phase information for these networks [36, 37] suggests that such networks are maintained through precisely timed functional interactions at various frequencies. Such a conception of brain functional networks is not yet sufficiently accommodated in the available analysis models. Another aspect that may be relevant for the understanding of the relation of baseline brain activity and the behavior and experiences of an individual is what determines the transition of one network state to the other, how these transitions are affected by external demands, and how they modify the content of our experiences and actions. Initial steps

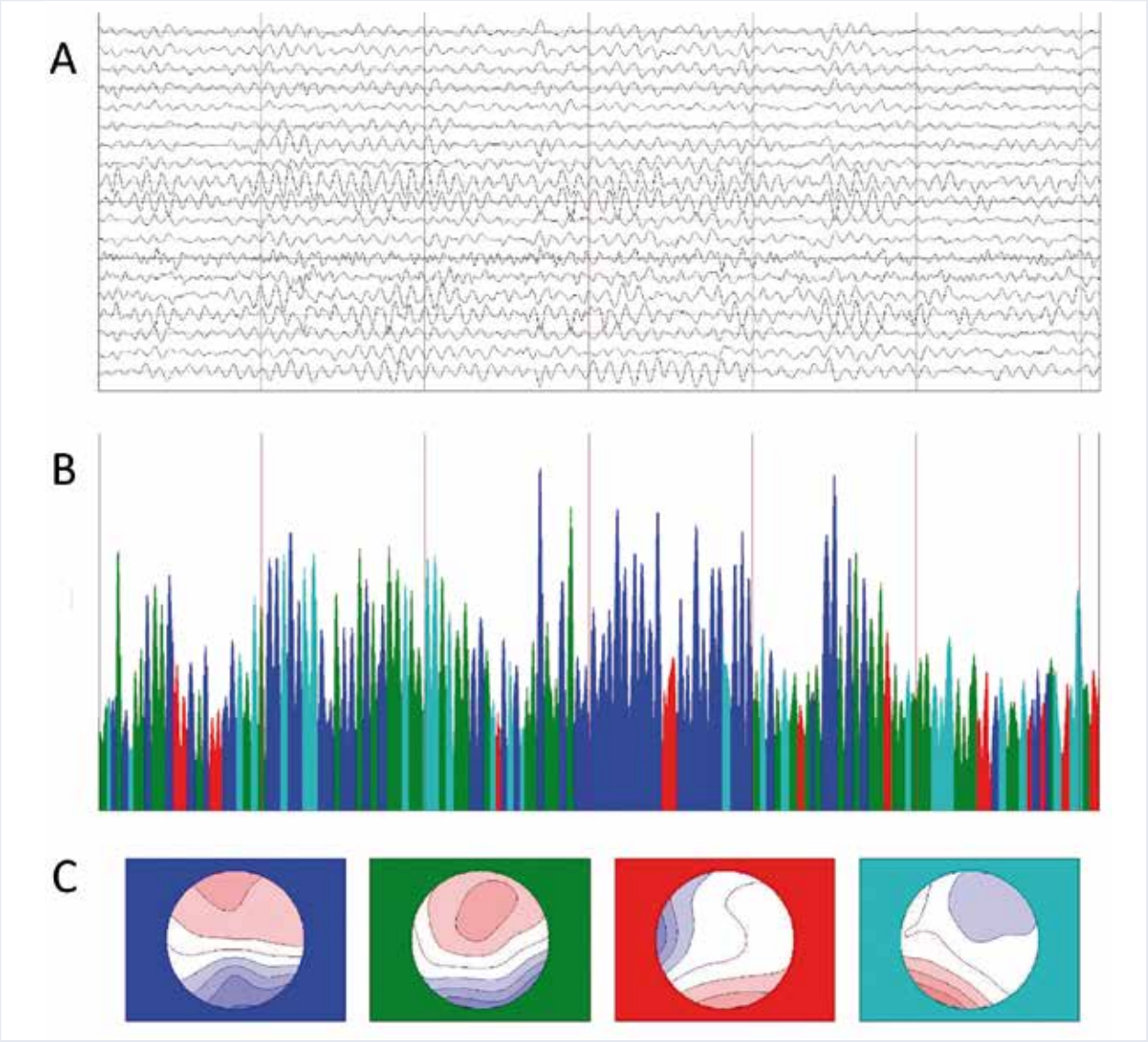

Figure 2: An example of a microstate analysis of spontaneous EEG. A: the EEG traces. B: The momentary Global Field Power (GFP), with colors indicating the assignment to one of the microstate prototype maps shown in C.

in such a direction have been done, e.g. in a recent study by Razavi and Jann [38], who showed in a simultaneous EEG-fMRI study that the EEG correlates of fMRI resting state networks were shifted to lower frequencies in their patients, indicating that the functionality of brain functional networks depends not only on the integrity of the involved nodes, but also on the proper modes of interactions among these nodes. The importance of the rules of state transitions at rest and following task demand has also been demonstrated, making a tentative causal link between at-rest abnormalities of default-mode network activity in schizophrenia patients and an insufficient recruitment of task relevant processing resources [39].

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Chemosensory Event Related Potentials

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Summary

Chemical senses comprise olfactory, gustatory and trigeminal (somatosensory) function. The chemosensory functions are still not fully understood. Consequently, the workup and understanding of chemosensory disorders is limited. With the present article we try to update the knowledge on human chemosensory disorders with a special focus on measurement of these functions.

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Key words: Taste, olfaction, trigeminal

Chemosensorisch evozierte Potenziale

Die chemischen Sinne umfassen neben dem Riechen und Schmecken auch den intranasalen und intraoralen Tastsinn. Die chemischen Sinne sind in ihrer Funktionsweise noch nicht ganz verstanden. Dementsprechend fehlt es derzeit noch an profundem Wissen über Ursachen, Abklärungen und Therapie chemosensorischer Störungen. Mit der vorliegenden Arbeit möchten wir eine kurze und aktuelle Übersicht zu den menschlichen chemischen Sinnen geben, wobei ein Fokus auf die Abklärung und Messung chemosensorischer Störungen gelegt wird.

Schlüsselwörter: Riechen, Schmecken, Trigeminus

Potentiels évoqués chémosensoriels

L'odorat, la gustation et le sens trigéminal intraoral et intranasal sont considérés comme étant des sens chimiques qui nous permettent la perception de signaux moléculaires. Le fonctionnement des sens chimiques n'est pas compris en détail, et par conséquent nos connaissances de prise en charge et traitement des troubles chémosensoriels sont en encore peu établies. La revue suivante essaie de faire un résumé des connaissances cliniques, en focalisant sur la prise en charge et les mesures des fonctions chémosensoriels.

Mots clés : Goût, odorat, trigéminale

Introduction

Before focusing on chemosensory event related potentials it is necessary to explain the chemical senses which are not familiar as such in the current language. Chemical senses are defined as human senses that allow us the decoding of molecular information surrounding us in our daily life. Most of these molecular stimuli are volatile such as odors or irritants perceived through the nose but might also be non volatile such as spices or tastants perceived orally. Having said this it becomes clear that the main organs for chemosensory perception are the nose or nasal cavity and the mouth or oral cavity. A closer look shows that three sensory systems are located within these two cavities giving rise to the chemical perception of inhaled and ingested air and substances respectively. Olfaction or smell, gustation or taste and somatosensation or trigeminal perception, are the three afferent systems commonly called chemical senses. Olfactory innervation is only present in a circumscribed area within the nasal cavity, the olfactory epithelium (**Figure 1**) that comprises the olfactory neurons that project to the olfactory bulb, the very distal enlarged part of the olfactory nerve (cranial nerve I). Taste innervation is only located within the oral cavity with the most dense innervations on the tongue and soft palate. Three cranial nerves convey gustatory fibers, the intermediate, glossopharnygeal and vagal nerve (cranial nerves VIIbis, IX and X), whereas none of them is an exclusive taste nerve. All the taste fibers coming from these three nerves converge to the nucleus tractus solitarius (NTS) located within

the brain stem. In contrast, somatosensory innervation is present in the nasal and oral cavity. Irritants or spices are consecutively perceived in the oral as in the nasal cavity. The overwhelming majority of smells cannot be perceived by the oral cavity as most basic tastes such as salt or sugar cannot be perceived by the nasal cavity. This is pointed out to familiarize the reader with the fact that the oral and nasal cavities are double sensory organs that perceive smells and irritants or both (nasal cavity) and tastes and spices (oral cavity) simultaneously. As most of the stimulations encountered in daily life such as during eating and drinking are composed of multiple chemical stimuli this makes it clear that it is not always easy to separate the stimulated chemical sense and to know which of the mentioned sense have been stimulated and to which extent. The possible co-stimulation and contamination by a second chemical sensory afference is probably one of the reasons why proper chemosensory testing has been an issue for many years and still is not yet part of clinical routine testing.

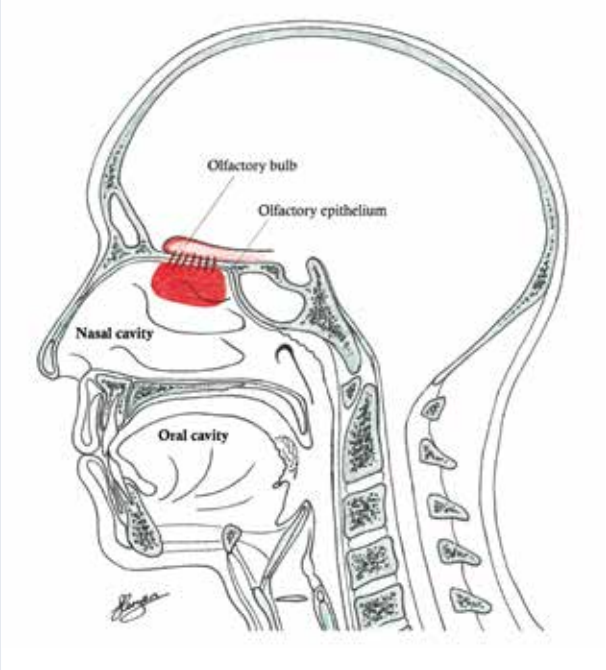

Figure 1: Sagital section showing the nasal cavity and the olfactory epithelium

Chemical Senses

The chemical senses have been explained in the introduction. What stimuli are these senses able to decode? An overview is given in **Table 1** showing that the olfactory system is the sense with the broadest range of perceivable stimuli [1]. The chemosensory trigeminal nerve is stimulated via TRP-channels that are activated by many molecular substances but also temperatures or touch. The overwhelming majority of molecules that we call odors are indeed substances that activate ORs as well as TRPs [2]. Only a handful of odors do selectively activate only ORs without doing so for TRPs [2 - 3]. Reaching a certain, high enough concentration even these "pure olfactory" substances become trigeminal meaning that they co-activate TRP channels [4]. The other way around only few substances selectively stimulate only TRPs and are consequently used for trigeminal testing. Taken together, the temperature, the molecular concentration and the kind of molecular substance are factors that influence chemosensory co-activation. It becomes thus clear, that it is crucial to stimulate the chemical sense we want to investigate in a very selective way by choosing not only the stimulus substance but also its concentration and temperature in order to avoid mixed chemosensory stimulation.

Central connections

As mentioned the three chemical senses show distinct differences in terms of receptors they express on their sensory nerve endings and the selectivity of the respective information is thus given. However, many substances are able to stimulate simultaneously receptors of the different modalities taste, smell and somatosensation. There is also considerable overlap in peripheral innervation of the oral and nasal mucosa [5 - 6] that makes it furthermore difficult to be selective in stimulation in an isolated way a given chemical sense. The three chemosensory afferencies are conducted to the central nervous system by very distinct cranial nerves. As shown in an adapted figure from Rolls [7] the sensory information of olfaction, taste and trigeminal origin converges within the central nervous system after only two or three synaptic changes. Although every sensory system has its own nerve fibers the chemosensory information of smell, taste and somatosensation becomes again, like at the peripheral level, intermingled at a cortical level [7 - 8]. This intimate relation at a central nervous level with bi- and trimodal neurons for smell, taste and touch at the level of the orbito-frontal cortex has [8] led to the assumption that the three chemical senses are differently related and influenced by each other than the other sensory modalities such as audition and vision. In contrast to compensatory mechanisms, often observed with the other non chemical senses in case of sensory loss (e.g. improvement of mechanical touch in blind) no similar mechanisms have so far been observed within the chemical senses. The current opinion is that sensory loss of one chemosensory modality often entails subclinical weakening of the other chemical senses. Numerous observations in healthy [9] and diseases [10] states seem to confirm this still controversially discussed [11] assumption.

Table 1: Overview of the chemical senses, their localization, types of receptors and the stimuli they can perceive.

	Olfaction / Smell	Somatosensation / Trigeminal Nerve	Gustation / Taste
Innervated organ	Nasal cavity	Nasal and oral cavity	Oral cavity
Receptors	Olfactory receptors (OR)	Transient Receptor Protein (TRP)-Channels	Taste Receptors (TR)
Recognition of	Unlimited number of odors	Numerous substances	Five basic tastes
	Substances stimulating only OR - Vanilla - H_2S (hydrogensulfide) - Phenylethylalcohol (rose odor)	Substances/stimuli stimulating only TRP - Acetone - Capsaicin (red pepper extract) - CO_2 (carbon dioxide) - Temperature (heat/cold) - Touch	- Sweet - Sour - Bitter - Salty - Monosodiumglutamate - MSG (Umami)
	Many substances stimulating two or all three sensory systems simultaneously (e.g menthol)		

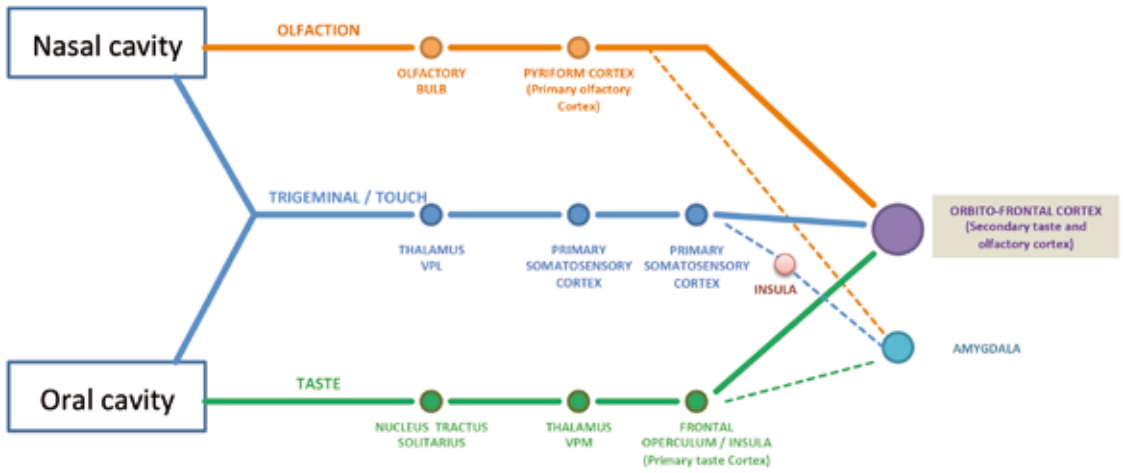

Figure 2: Overview of the pathway from periphery to central connections of the three chemical senses.

Chemosensory disorders

Compared to hearing or vision loss, the impairment or loss of any of the chemical senses has less obvious and visible consequences for social functioning. However, any of the chemical senses' dysfunctions has clear and sometimes very handicapping consequences [12] and they should no longer be considered minor or neglected senses [13]. Besides decreased pleasure for food, the lacking of meaningful odors such as that of beloved persons or situations may lead to major mood changes [14]. Besides these painful experiences of missing the olfactory world, invariably all patients concerned of olfactory loss experience hazardous events such as eating spoiled food or non detection of smoke or gas leaks [15 - 16]. This shows at which point chemical senses serve as alarm system since even persons who could adapt to the lack of one of these systems such as congenital anosmics do not really overcome the increased risk of hazardous events [17]. The three chemical senses are not equally often concerned by dysfunction. While olfactory impairment is very prevalent within the general population [18 - 19] as well as in specialized outpatient clinics [20], taste disorders are far less frequently encountered [21 - 22] and intranasal and intraoral trigeminal disorders are not well investigated and no reliable data concerning its prevalence in the general population or in specialized outpatient clinics are yet available. The most frequent types and reasons for smell, taste or trigeminal loss or impairment are summarized in **Table 2**.

Assessment of chemosensory function

Similarly to other sensory systems it has first of all to be decided if there is a qualitative or quantitative

Table 2: Overview of the most frequent causes for olfactory, gustatory or trigeminal impairment.

Chemical Senses – Disorders and Causes

	Olfaction / Smell	Somatosensation / Trigeminal Nerve	Gustation / Taste
Type of disorder	Quantitative Disorder Anosmia = total loss Hyposmia = deceased perception Qualitative Disorder Parosmia = triggered distortion Phantosmia = not triggered deceased	Quantitative Disorder Anaesthesia = total loss Hypaesthesia = deceased perception Qualitative Disorder Paraesthesia= prickling, tingling Dysaesthesia = distorted sensory perception	Quantitative Disorder Ageusia = total loss Hypogeusia = deceased perception Qualitative Disorder Parageusia= triggered taste distortion Phantogeusia = not triggered distortion
Most frequent causes of disorder	Sino-nasal disorder Posttraumatic Post-infectious (upper respiratory tract infection) Neurodegenerative diseases Toxic exposure Congenital Absence Idiopathic	Postoperative - Trauma Toxic exposure Medication side effects Neuropathies /Neurological Metabolic diseases Idiopathic / Burning mouth syndrome	Postoperative / Nerve lesions Post-infectious Medication side effects Metabolic / Systemic diseases / Deficiencies Posttraumatic Idiopathic / Burning mouth syndrome
Recovery / Treatment	Depending of the cause. Poor recovery for posttraumatic. Excellent recovery in postinfectious or sinunasal causes Treatments: - Smell training - Spontaneous recovery - Nasal steroids / Surgery	Poor knowledge on recovery of trigeminal disorders. Similar to that of peripheral nerve lesions. Relatively good spontaneous recovery depending on the extent of the nerve lesion. Treatments: - Spontaneous recovery	Depending of the cause. Overall good recovery for most causes. Treatments: - Spontaneous recovery - Treating underlying cause - Substitution of deficiencies - Medication discontinuation -Zinc

dysfunction or both are present (**Table 2**). To take audition as example, this would mean to distinguish between a tinnitus (qualitative disorder) or hearing loss (quantitative disorder). Exactly as for other sensory modalities (e.g. audition), quantitative chemosensory disorders are measurable whereas qualitative disorders are not measurable [23]. As for every sensory modality there is an objective and psychophysical way to assess chemosensory function. The psychophysical tests for olfaction, taste and trigeminal function have been developed to a very different extent and are quickly overviewed. The big advantage is the easy handling and the relative little time consumption which makes psychophysical attractive for clinical use. However, these tests often lack absolute precision and are prone to diverse biases reaching from the patient's collaboration and motivation to verbal confusion and patient's comprehension as well as the tester's experience [24]. It is therefore especially important to have objective tests such as chemosensory event related potentials to assess chemosensory function with more precision and less biases.

Psychophysical tests

Why is testing of chemical senses important at all? Different reports show that neither for olfaction nor for taste self rating of the respective sensory function by the patient is reliable [25 - 26]. It is thus mandatory to test chemosensory functions by means of tests rather than to simply ask about how people consider their chemical senses.

Olfactory tests

Olfaction has probably been the most explored of the three chemical senses with first testing procedure proposed for over a century ago [27]. It is only a little more than 30 years that a breakthrough in clinical and psychophysical olfactory evaluation has been achieved with the establishment of the forced choice identification procedure [28] and the development of easy to handle and re-usable tests which could be reproduced everywhere [29]. The last twenty years have been marked by an amazing amount of literature and increase of clinical knowledge regarding olfactory function in humans. This has been largely possible due to psychophysical tests that could be used in different populations simultaneously with multicenter studies and large sample sizes. One of these very widespread tests is the European Sniffin'Sticks test battery [30]. There are worldwide many test devices that have more or less been well validated, whereas only few tests offer available normative data based on large observations [20, 31].

Gustatory tests

Although taste as modality seems much easier since it comprises only five basic tastes the testing devices and their standardization have been a problem for many years. First efforts to have a uniform and reproducible taste testing were done by two different means. Some authors concentrated on electrical taste testing [32], which consists of application of electrical current to the tongue, eliciting a tingling and sour prickling sensation. Although there is a debate about how much of this sensation is trigeminal and how much gustatory it is meanwhile accepted that this electrogustometry reflects to some extent gustatory function [33]. The second way of testing was by means of chemical stimuli (e.g. sugar, salt) which is probably a more taste specific stimulation but a little more time consuming since all tastes need to be tested. One of the first methods was the three drop method [34] which has been replaced by the Taste Strips [35], a filter based test device that fulfils the criteria of easy to handle and reproducible gustatory testing with meanwhile normative data available [36]. However, there are still improvements possible for psychophysical taste testing since the current methods still lack the possibility to test for routine taste thresholds or umami, the fifth taste.

Somatosensory/Trigeminal tests

Measuring intranasal and intraoral trigeminal somatosensation is still difficult and only practiced in specialized Smell and Taste Clinics. It is the least well investigated chemical sense in terms of available psychophysical test devices. This is partly due to the fact that olfaction and taste seemed more interesting for the chemosensory community and avoiding trigeminal contamination was more important than trigeminal examination itself [2]. Further, for probably many years it was not clear what importance trigeminal testing might have in a clinical setting. Meanwhile things change and testing trigeminal function (intranasal and intraoral) has become very interesting especially for clinicians since it is speculated that trigeminal function largely contributes to airflow perception and feeling of nasal patency and thus well being during breathing [37]. Thus, altered trigeminal function might have direct clinical consequences with patients complaining of nasal blockage. Recent studies suggest that patients with low intranasal trigeminal function may be more prone to get nasal surgery than those with better trigeminal function [38]. To investigate such findings it is necessary to have adequate tools. It is only very recently that reliable psychophysical test devices have been developed. These tests use either pure trigeminal active substances such as CO_2 [39 - 40] or the principle of lateralization [41]. Lateralization uses the fact that molecular stimuli that trigger exclusively olfactory receptors without trigeminal co-stimulation (e.g. vanilla) cannot be localized reliably to the side of application if they are given to either the left or right nostril. The more the used substance is also stimulating trigeminal receptors (e.g menthol) this localization becomes reliable [4]. Due to this relatively new test devices and their availability, it is likely that more knowledge on intranasal trigeminal function will be coming up in the years to come.

Objective tests

Psychophysical tests for chemosensory functions have many limitations. Testing children is difficult especially below a certain age where collaboration is limited. The same is the case for malingerer's simulating a smell, taste or trigeminal loss as well as unconscious and dement patients. Further, psychophysical measures lack a certain precision to measure very subtle modifications that might be measurable with more objective tests. The need for objective test devices for chemical senses is thus obvious. Functional imaging techniques based on either functional magnetic resonance imaging (fMRI) or positron emission tomography (PET), have been used to assess objectively olfactory function [42 - 43]. Both techniques show a varying degree of spatial resolution but a rather poor temporal resolution. This is mainly due to the fact that they measure metabolic changes in the active brain regions, rather than measuring direct electric brain activity. Thus, the signal to noise ratio is very high and both techniques are not yet meaningful in the clinical workup of individual patients and both techniques are mainly used in research.

Chemosensory event related potentials

Olfaction and Trigeminal ERP

Event-related potentials are EEG-derived poly-phasic signals. They are caused by the activation of cortical neurons which generate electro-magnetic fields. As the EEG is a noisy signal which contains activity from many cortical neurons, ERP need to be extracted from this background activity. The classical approach to this problem involves averaging of individual responses to olfactory stimuli such that random activity would cancel itself out while all non-random activation would remain. Olfactory ERP (1) are direct correlates of neuronal activation, unlike the signals that are seen, for example, in functional MR imaging, (2) have an extremely high temporal resolution in the range of micro-seconds, (3) allow the investigation of the sequential processing of olfactory information, and (4) can be obtained independently of the subject's response bias.

Olfactory and trigeminal event related potentials were developed more or less at the same moment.

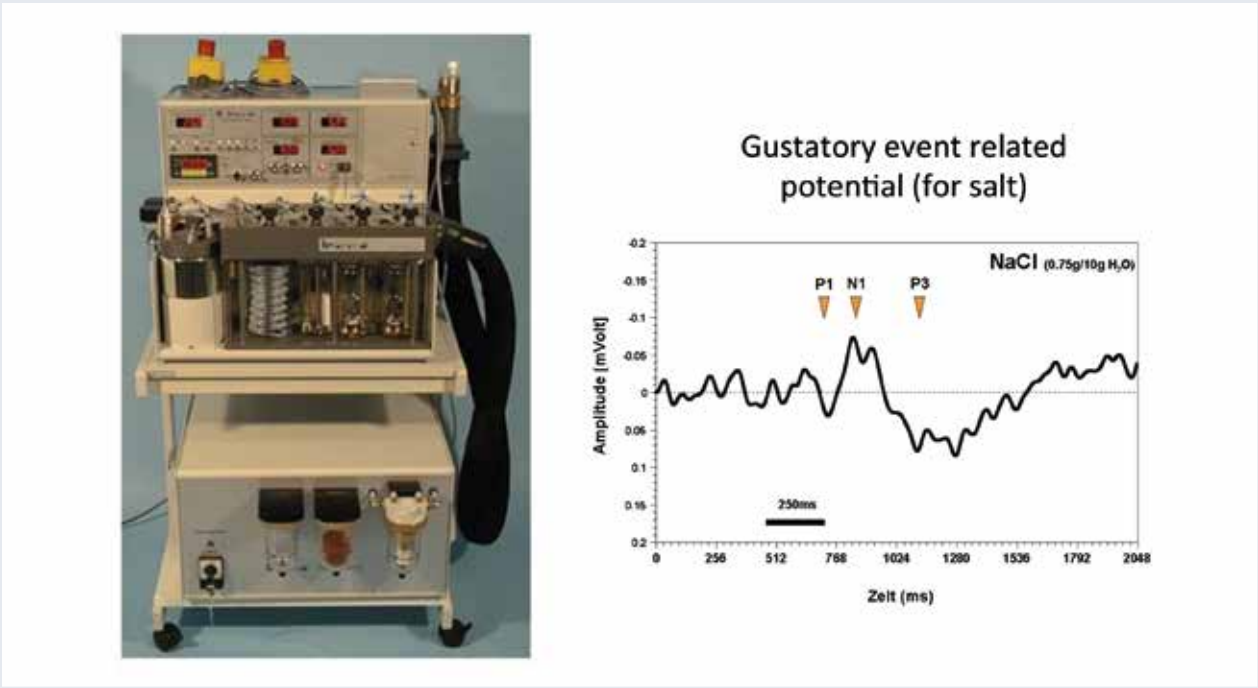

Figure 3: Olfactometer and typical curve of normal event related potential to a gustatory stimulus.

Compared to auditory and visual ERPs, which were recorded much earlier, olfaction and trigeminal ERPs have reliably been recorded only in the beginning of the 1980ies [44]. The major problem to overcome was to produce a stable stimulus that did not contain possible contamination by the other chemical sense of the nasal cavity. Since the nasal cavity perceives odors and somatosensation, a simple odor puff applied into the nose would stimulate olfactory nerves but the sudden airflow change (puff) would also produce a trigeminal/touch response which would then add some somatosensory response. The solution was brought up by Kobal who developed an olfactometer that made it possible to produce an olfactory or trigeminal stimulus that is embedded in a constant airflow of constant humidity and temperature [44]. Based on a valve system built into the nosepiece of the olfactometer, it is possible to change from a trigeminal to an odor stimulus within less than 50 ms. The stimulus for each modality is specific with trigeminal event related potentials being generated with CO2 as stimulus and olfactory ERPs generated with H2S, vanilla or rose odor (Phenylethylalcohol). The olfactometer is unfortunately and still nowadays not a small and easy to transport box but resembles middle size lab equipment (**Figure 3**) and measurements are relatively time consuming. However, in contrast to fMRI and PET CT, the trigeminal and olfactory event related potentials have found their way into clinical workup. Olfactometers are still quite expensive and their use is currently not as user-friendly as this is known from other electronic products. As consequence olfactory and trigeminal potentials are mainly used in specialized Smell and Taste Clinics and for special mostly assurance and expertise questions. Regardless of the restricted routine use in clinics, olfactory and trigeminal event related potentials have helped to understand many aspects of these two chemical senses [45]. Particularly the exact interaction and mutual interaction between olfaction and trigeminal stimuli as well as the precise measuring of olfactory function in small children has been possible with olfactory and trigeminal event related potentials [46]. The same is the case for precise assessment of olfactory deficits in mild cognitive impairment [47]. Recently, it has been shown, that olfactory ERPs also predict recovery after olfactory impairment [48].

Recent developments in electric source localization made it even possible to identify deep brain generators, which were so far only identified by fMRI [49].

Gustatory ERP

In contrast to olfaction where objective measurement methods have been developed two decades ago and are currently integrated into clinical workup, objective taste measurement remained for very long an experimental tool. Similarly to olfaction, taste function can be assessed by means of functional imaging such as fMRI and PET. The literature and the number of studies on functional gustatory imaging is however relatively little compared to that on olfaction [50 - 54]. These techniques are yet still restricted to research and are not used in clinical workup of patients. The same is true for magnetic encephalography (MEG), which has been a very elegant tool to unravel and confirm the gustatory central nervous cortices [55 - 58] but is not yet a clinically used instrument.

Gustatory evoked potentials (GEPs) have been successfully recorded the first time in 1985 by Kobal [59]. However, mainly for technical reasons GEPs have not been continued and it is only 20 years later that we tried again to reactivate this technique, showing its clinical feasibility [60]. Some technical difficulties could be overcome but considerable problems and shortcomings persist in the way Kobal proposed the recording of potentials. A recent approach with a gustometer based on water-diluted stimuli (in contrast to air-diluted stimuli) showed the feasibility of this technique and first published articles are promising [61 - 63]. Future work will have to focus on the clinical use of gustatory event related patients with taste disorders.

Future outlook

Within the field of chemical senses we are now at the point where we have a considerable but still insufficient knowledge on causes, recovery rates and psychophysical assessments of smell, taste and to a certain extent also trigeminal function. However, many aspects of the chemical senses are poorly understood. Especially measurement techniques and particularly objective measurements are now possible but not used in a widespread way manly because of cost and time reasons. It will be a clear future issue to improve the available techniques or bring up new possibilities of objective measuring. One of these new techniques is the frequency analysis of cortical response to chemical senses which opens potentially the door to very easy objective assessment of olfactory, taste and trigeminal function. First steps have shown its feasibility [64 - 65] and it will be interesting to see if this new method can be improved and simplified sufficiently to find its way into clinical routine use.

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