

Olfaction as One of the Key Components of the Neuropsychological Examination

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Обоняние как один из ключевых компонентов нейропсихологического исследования

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Abstract. Olfactory deficits are common among non-clinical and clinical patients, particularly in those with neuropsychological conditions. They are, however, often not diagnosed because standard assessments focus on superior cognitive domains and do not examine the senses. Olfactory function greatly impacts mental health and quality of life. It is also associated with the likelihood of developing neurological or psychological conditions and impacts the prognostic and rehabilitative outcomes of patients, particularly in regards to cognitive health. The purpose of this article is to (a) provide an overview of the olfactory sense and its unique characteristics, (b) discuss the scientific literature around olfaction and related neurological and psychological conditions, (c) present common olfactory assessment techniques, and (d) argue for the inclusion of olfactory measures to standard neuropsychological examinations. An olfactory measurement tool is currently being developed that is suitable to supplement neuropsychological examinations.

Keywords: *olfactory sense; neuropsychological assessment; olfactory test; anosmia; hyposmia; neurological health; psychopathologies; brain impairment; cognition*

Аннотация. Нарушение обоняния часто встречается у неклинических и клинических пациентов, особенно у пациентов с расстройствами нейropsychологического характера. Однако его сложно диагностировать, поскольку стандартные тесты сфокусированы на диагностике высших когнитивных областей и не определяют состояние органов чувств. Функция обоняния оказывает большое воздействие на психическое здоровье и качество жизни. Она также может указывать на вероятность развития неврологических или психологических состояний и влиять на прогностические и реабилитационные результаты пациентов, особенно в отношении когнитивного здоровья. Цели данной статьи: (а) ознакомить с результатами теоретического изучения феномена обоняния и его уникальных характеристик; (б) представить обзор научной литературы, посвященной обонянию и связанными с ним неврологическими и психологическими состояниями; (в) показать наиболее распространенные методы диагностики обоняния; (г) доказать необходимость включения оценки обоняния в стандартную процедуру нейropsychологического исследования (в настоящее время ведется разработка инструментария).

Ключевые слова: *чувство обоняния; нейropsychологическая оценка; диагностика обоняния; потеря обоняния; понижение обоняния; неврологическое здоровье; психопатологии; поражение мозга; когниция*

Introduction

Approximately one fifth of the world's population suffers from an olfactory disorder (Croy, Nordin, & Hummel, 2014). Olfactory deficits, known as anosmia, are common results of brain disorders affecting 10–66.8 % of those who experienced brain trauma (Drummond, Douglas, & Olver, 2013). Only a minority of patients who underwent neurological traumas and have consequential olfactory shortcomings, nonetheless, are

aware of such deficits (Callahan & Hinkebein, 2002). This could be because standard neuropsychological examination measures, such as the Mental Status Examination (Martin, 1990) and the Glasgow Coma Scale (Teasdale & Jennett, 1976), cover cognitive and executive functioning but occlude sensory perception. Thus, olfactory deficits are often not brought to the awareness of patients or their healthcare providers. There is a lack of universal clinical practice guidelines for the detection of olfactory dysfunction (Miwa et al., 2019). In the present article, we examine the scientific literature around olfaction, olfactory deficits, and how olfactory dysfunctions relate to neurological, neuropsychological, and other health disorders. Common olfactory assessment strategies are hereby introduced and discussed through Lurian and Neurolurian paradigms. Olfactory rehabilitation and its potential to improve neurological functioning, prognosis, and quality of life are considered. Lastly, we argue for the addition of olfactory measures to standard neuropsychological examinations.

The Olfactory Sense

Olfaction is a highly instinctive component of the human experience. Scliar (2020) refers to it as a “nasal instinct” that is, probably, the most ancient of the five senses. Smells are believed to be first perceived unconsciously by archaic brain structures, away from the neocortex. The symbolic nature of olfaction is well understood by photographers who capture politicians with their fingers in their noses. This induces an automatic feeling of disgust in the spectator due to the evolutionary function of olfaction: to protect against the dangers of ingesting rotten food or the exposure to noxious substances; when something has an unwholesome smell, we instinctively obstruct our nostrils, either with our hands or by shrinking our faces.

Both sensation and perception are connected to the lived experience. According to Gazzaniga and Heartherton (2005), perception involves the processing, organization and interpretation of sensory stimuli captured by sensation. It is the result of conscious experiences that allow for the attribution of meaning to a given sensation. While bottom-up processing is based on the physical characteristics of the stimulus, top-down processing rests on how we interpret the captured information through our knowledge, expectations, and experiences. Our sensory systems for each of our senses — olfaction, gustation, vision, audition, and tactile — translate the physical properties of stimuli into neural impulses through sensory coding (Ibid.). Two additional senses are now also considered: vestibular (movement) and proprioception (body position). Along with gustation, olfaction is a chemosense originated when chemical stimuli, i.e., odorants, bind to chemoreceptors. The olfactory mucosa is so sensitive that few molecules are sufficient to stimulate it, producing an odor sensation. The sensation will be greater with more stimulated receptors, which depends on the concentration of odorous substances in the air. The receptors involved in olfaction and gustation regenerate every sixty days and new ones arise after two months (Martin, 2013).

Olfactory information is processed in the most archaic part of the brain, the rhinencephalon, a word of Greek origin that translates into: “smell” and “brain.”

Odor particles enter the rhinencephalon and meet receptor neurons in the olfactory mucosa whose axons form the olfactory nerve bundle and synapse in the olfactory bulb. Information subsequently reaches the primary olfactory cortex (POC) found in the prefrontal cortex, where elemental olfactory information begins to be processed (Silveira-Moriyama et al., 2016). The rudimentary rhinencephalon has few connections with brain zones that, from an evolutionary point of view, have more recent origins, such as the neocortex, where the centers of language are found (Scliar, 2020). The rhinencephalon is associated with ancient brain structures such as the limbic system, highly involved with emotions and memory, and the pituitary gland which is an important component of the hormonal system (Ibid.). It is, thus, not by chance that olfactory stimuli also evoke feelings and recollections.

The Subconscious Quality of Smells

We find it easier to describe appearances, sounds or tastes than smells. In addition to the scarcity of vocabulary dedicated to odors, there is a difficulty in consciously attributing emotions to smells, something that does not happen as strongly with other senses such as sight and hearing. We speak, for example, of ‘intimidating,’ “comforting” appearances or noises, but restrict ourselves to simple adjectives such as “pleasant” and “unpleasant” to report odors. This may be due to the fact that olfaction is more unconscious than the other senses. Developmental research indicates that the ability to detect smells is established prenatally. Exposure to prenatal odor through amniotic fluid has been found to significantly affect odor-mediated behavior after birth (Ciccotti, 2010). Newborns of mothers who ate foods with anise during their pregnancy had positive reactions sucking, attempting to touch, and chewing to the anise odor. Newborns whose mothers had not consumed anise had more aversive reactions to the odor — furrowing of the nose and eyebrows, mouth arching downwards, and head movement (Ibid.).

As highlighted by Scliar (2020), the perception of smells arises prior to the ability to express oneself verbally. As a result, we have strong emotions and reactions in response to different odors, however, lack the means to verbally discuss such instinct-driven experiences. In this way, before we can rationally examine a given smell and translate it into words, we act instinctively, automatically in response to the stimulus. In light of the evolutionary process this is understandable as instinctive reactions saved the life of the primitive man who sniffed an approaching beast by activating the simple and binary “fight or flight” reaction. Additionally, some olfactory receptors detect pheromones which are chemical substances emitted by beings of the same species that, for example, stimulate an instinctive sexual approach.

Research on the relationship between smell and cognition points to a possible existence of olfactory memories that are independently constituted, autonomous and non-reliant on superior cognitive skills (e.g., Danthiir, Roberts, Pallier, & Stankov, 2001). Zucco (2003) found that distracting interferences do not impact the recognition of olfactory materials. It is hypothesized that odor recollection is given through a memory system separate from the remaining senses with the assumption that (a) odor stimuli do not

induce conscious representations of themselves, and (b) odor memories can be stored at a subconscious level. This means that a person exposed to an odor would first become conscious of the smell, during memory encoding, then, once the stimuli is removed, have no conscious representation of it. The odor would be implicitly and effortlessly stored in memory without the person's conscious awareness (Ibid.). This argues for a potential of olfactory tests to investigate neuropsychological states of those with impaired awareness and cognition that are unresponsive to stimuli that require greater cognitive engagement.

Olfaction and Health

Odor exposure has been found to induce changes in brain electrical activity correlated with attention (Martin, 2013) and to improve correct recollection of events that took place years earlier (according to Aggleton and Waskett, as cited in Martin, 2013). Smells have also been shown to enhance pain perception (Martin, 2006). Olfaction is directly linked to safety and quality of life. Disturbances around smell are known to possibly lead to significant impairments in important domains such as the ability to detect harmful chemicals and smoke, as well as to taste and enjoy food and maintain healthy eating habits (Croy et al., 2014; Hummel & Nordin, 2005). It can also compromise social interactions, affect mood, and contribute to anxiety, feelings of isolation, and / or depression (Croy et al., 2014).

Olfactory dysfunctions are prevalent among the general population and even more common in clinical samples. They are tightly associated with different neuropsychological conditions, however, largely unconsidered in clinical settings; they are not a component of standard neuropsychological examinations. As a result, patients and healthcare providers remain unaware of olfactory issues and how they relate to the clinical condition at hand. We hereby provide an overview of olfaction in brain health to illustrate the importance of considering olfaction in clinical neuropsychological examinations.

Olfaction in Neurological and Neuropsychological Conditions

Olfaction and Psychopathologies

Neural structures involved in the processing of olfaction are tightly connected to limbic structures in which emotional processing takes place. As previously discussed, both structures are considered rudimentary in that they are evolutionarily more primitive than other parts of the human brain. This suggests that olfaction and emotion were both primordial functions in development. Moreover, olfactory and emotional functioning share key structures such as the amygdala and the hippocampus responsible for admitting and processing incoming environmental signaling (Croy & Hummel, 2017). They receive “raw” olfactory information that bypasses the thalamus and are crucial for determining the emotional load attributed to whatever is captured from the environment. Given the independent and subconscious path of olfactory information, it is believed that odors can elicit corresponding emotive states before they reach consciousness (Ibid.).

Notably emerging research indicates that affective disorders, especially depression, may lead to decreased activation and volume in olfactory structures in the brain, particularly in the olfactory bulb. Conversely, the olfactory bulb could serve as an indicator of greater susceptibility for the development of depression (Ibid.). Research by Rottstaedt et al. (2018) found that psychiatric patients had a significantly reduced olfactory bulb — 13.5 percent smaller than control. Additionally, olfactory bulbs reduced in size anticipated major depression in 70 percent of cases.

The intimate anatomical and functional associations between emotion and olfaction are thought to explain why they are often simultaneously compromised. It has been, for example, observed that those with anosmia — lack of olfactory abilities — are more likely to show symptoms of depression than those who do not have anosmia (Croy & Hummel, 2017). Conversely, subjects with depression score lower on olfactory tests measuring odor identification, discrimination, and sensitivity (e.g., Lombion-Pouthier, Vandel, Nezelof, Haffen, & Millot, 2006). Interestingly, Lombion-Pouthier et al. (2006) also found that depressed people have a tendency to overestimate the pleasantness of odors. The dynamics between olfactory and mental disabilities vary according to the psychological condition at hand. Unlike depression, anorexia nervosa was found to increase subjects' sensitivity to odors making them judge those as more intense but less pleasant. Those with alcohol or other drug addictions had significant difficulties in identifying odors (Ibid.). Moreover, smell identification deficits are a typical feature of early onset psychosis as well as of cognitive deficits and negative symptoms in schizophrenia (Corcoran et al., 2005). A review of the scientific literature focused on affective and anxiety disorders found no olfactory deficits in most people with bipolar disorder (Burón & Bulbena, 2013). Odor identification issues were notably present in people with post-traumatic stress and obsessive-compulsive disorders (Ibid.). Burón and Bulbena (2013) concluded that examining olfaction could be an effective supplementary tool to better understand psychopathological conditions.

Olfaction in Neurological and Neurodegenerative Conditions

Olfactory deficits are common in an array of neurological and neurodegenerative conditions such as cerebrovascular accidents, traumatic brain injuries and dementias (e.g., Aliani et al., 2013). Reduced sensibility to odor — hyposmia — is a major symptom of Parkinson's Disease (PD) present in approximately 90 percent of early-staged cases (Xiao, Chen, & Le, 2014). The gradual loss of smell is considered a predictor of the development of PD. Therefore, investigating this sense can collaborate with early and more accurate diagnoses. The observation that olfactory deficits manifest themselves prior to other symptoms of PD led to the hypothesis that the initial causative event for the development of the disorder takes place in the rhinencephalon — olfactory region — before the basal ganglia becomes affected (Hawkes, Shephard, & Daniel, 1999). Hyposmia and anosmia are studied as potential biomarkers for different brain-based disorders; examining olfactory symptoms in neurological conditions could help clarify their underlying pathological mechanisms (Xiao et al., 2014).

Despite few publications on olfaction in patients with cerebrovascular disease, it is accepted that, to some extent, hyposmia occurs. The limited number of post-stroke olfactory studies generally report olfactory impairments more often than complete olfactory loss (Omori & Okutani, 2020). Conversely, olfactory recovery interventions are a promising rehabilitation strategy for those who suffered a stroke (Wehling et al., 2015). Olfactory assessments are also commonly used in neurological clinics to help identify possible cognitive decline in stroke patients or in those with other neurological disorders (Dulay, Gesteland, Shear, Ritchey, & Frank, 2008; Makizako et al., 2014; Ryo et al., 2017; Westervelt, Bruce, Coon, & Tremont, 2008).

Impaired olfaction has also been found associated with worsened prognostic outcomes of neurological complications. Callahan and Hinkebein (2002) established that people who suffered Traumatic Brain Injuries (TBIs) performed better cognitively when in the absence of smell dysfunctions. Anosmic patients had lower executive skills and were more functionally impaired than their non-anosmic counterparts. Comparative scores on neuropsychological measures of executive abilities (the University of Pennsylvania Smell Identification Test (UPSIT) and the Disability Rating Scale (DRS)) indicated that poor olfaction poses a risk for successful post-traumatic rehabilitation (Callahan & Hinkebein, 2002). Those with smell dysfunction experienced longer coma periods as well as greater deficits in memory, learning, complex attention, and problem solving (Ibid.).

There also is evidence to support a relationship between decreased olfaction and worsened prognosis of people at risk for Alzheimer's Disease (AD) and other dementia-related conditions. In spite of the need for a stronger body of findings, olfactory dysfunction has the potential to be a more significant indicator of prospective neurodevelopmental diseases than standard neuropsychological assessments (Martin, 2013). A systematic review by Sun, Raji, MacEachern, and Burke (2012) focused on the benefit of using olfactory identification tests as prognostic tools for AD and dementia. In one of the highlighted studies, Mild Cognitive Impairment (MCI) was longitudinally observed to lead to AD more often in the presence of poor olfactory performance; subjects with better olfactory identification abilities were less likely to progress from MCI into AD (Devanand et al., 2008; Sun et al., 2012). Moreover, Morgan, Nordin, and Murphy (1995) studied olfaction in people diagnosed with probable and questionable AD. They compared odor and picture identification capacities and found that odor identification was more strongly compromised than picture identification among subjects with probable and questionable AD. Morgan et al. (1995) concluded that the sense of smell can be a key diagnostic tool for AD that could improve the current neuropsychological assessment procedures.

Olfactory Loss in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)

Approximately one in every four patients admitted with SARS-CoV-2 self-reported issues with perceiving smells (according to Giacomelli, as cited in Hornuss et al., 2020). Research by Hornuss et al. (2020), nonetheless, indicates that the negative impacts of the virus on olfaction might be greater than perceived by the patients; the objective Sniffin' Stick

Test revealed that both anosmia and hyposmia were significantly more prevalent than patients subjectively recognized. Forty four percent of people categorized as having no olfaction (anosmia) and half of those with compromised abilities (hyposmia) did not recognize that they had olfactory deficits (Hornuss et al., 2020). The researchers, thus, stress the important role of objective olfactory measurements in the evaluation of clinical presentations of SARS-CoV-2 patients (Ibid.).

Beyond being one of the symptoms of SARS-CoV-2, olfactory dysfunction serves as a precursing clinical sign of a developing infection (Li, Bai, & Hashikawa, 2020); difficulty detecting smells tends to appear prior to other symptoms such as cough and fever. Moreover, Li, Long, et al. (2020) found that olfactory impairments can hold for longer than 95 days with a median duration of 62 days. Even though hyposmia tends to fade away within a couple of days upon healing from the infection, which was true for 44 % of studied Europeans (Lechien et al., 2020), some patients continue to have long-term impairments upon discharge (Li, Long, al., 2020).

Notably, the olfactory loss in SARS-CoV-2 is present in the absence of nasal obstruction and, thus, cannot be explained as resulting from a mechanical blockage of the olfactory pathway (Parma et al., 2020). Viruses that affect the Central Nervous System (CNS) are commonly neurotropic, such as measles virus and human immunodeficiency virus (HIV), however, respiratory viruses, such as influenza and coronaviruses, have progressively become a neuropathological threat (Bohmwald, Galvez, Ríos, & Kalergis, 2018). Respiratory viruses have been identified in the Cerebrospinal fluid indicating that, upon reaching the lungs, such viruses can infiltrate the CNS (Ibid.). SARS-CoV-2 is thought to have a disturbing effect on sensory-neural systems given its multimodal effect of impacting both olfaction and gustation and altering chemical sensitivities of membranes (Parma et al., 2020).

Olfactory neurons are considered possibly involved in the anosmic experience by acting as a portal for the entry of the SARS-CoV-2 virus (Hornuss et al., 2020). Other coronaviruses, including SARS-CoV, are known to have a high capacity of neuroinvasion (Ibid.). Given the similarities between SARS-CoV and the newer version of the virus (SARS-CoV-2), it is hypothesized that the latter could also impact the CNS. Characteristic clinical manifestations of SARS-CoV-2 — headaches, nausea, and vomiting — could indicate neurological impacts of the infection (Li, Bai, et al., 2020). Conversely, research by Mao et al. (2020) tentatively found that 36.4 % of SARS-CoV-2 infections came with neurological expressions. Neurological manifestations were more common in severe SARS-CoV-2 cases and included impaired consciousness (14.8 %), cerebrovascular diseases (5.7 %), and skeletal muscle injury (19.3 %). The neurological implications of the new coronavirus are, nonetheless, not yet fully understood and more research is needed. Particular attention should be given to the routes through which the respiratory virus reaches the CNS as well as to the long-term consequences of a neuroinvasion. When it comes to the guiding theme of this research, it is important to note that SARS-CoV-2 is another medical condition that is better understood with insights from olfactory assessments.

Olfactory Plasticity and Neuropsychological Rehabilitation

The neurological plasticity of the human brain has been extensively investigated in recent decades (Goldstone, 1998). Neuroplasticity can be observed not only after functional loss due to stroke, brain tumors or sensory deprivation (Merabet & Pascual-Leone, 2010) but also following the acquisition or optimization of sensory function with learning (Gilbert & Sigman, 2007). The olfactory system exhibits great changeability, due to mechanisms that have been extensively investigated both at cognitive and cellular levels (Mainland et al., 2002). A recently published study indicated that human olfactory acuity, as well as the primary representations of cortical odor, persist at normal levels despite acute nasal occlusion (Kollndorfer et al., 2014). These normal levels of performance are presumed to be maintained by top-down compensatory systems made possible by the neuroplastic quality of the brain.

The mechanisms of neural plasticity in the olfactory system are of particular interest given that losses or reductions in olfactory function are prevalent in many neurological and psychiatric conditions. As discussed in previous sections, smell loss is among the first symptoms of neurodegenerative disorders, such as Alzheimer's or Parkinson's disease. Olfactory deficits greatly impact quality of life and become especially debilitating when coupled to other sequels of brain injuries and disorders such as impaired cognition, sensation or motion (Drummond et al., 2013). Thus, neural plasticity in relation to olfactory dysfunction can have widespread implications for brain function far beyond olfactory perception. Olfactory rehabilitation is crucial for neurological functioning, prognosis, and quality of life. Thanks to the neuroplastic nature of the brain, the capacity to detect odors is changeable and one can learn to detect a particular smell through olfactory training (e.g., Cain & Gent, 1991).

In a study by Pistoia et al. (2015) a participant in a minimally aware state subjected to an olfactory imagination task was able to develop his conscious awareness skills upon a series of trials. The improvement most likely resulted from the training he received by repeating the olfactory-imaginative exercise which induced the patient to learn and develop a previously lacking ability. Olfactory training was found successful in the rehabilitation of people suffering from post-traumatic olfactory dysfunction. A randomized control trial training was administered for five minutes daily with four odorants (rose, eucalyptus, lemon, and cloves) during 16 weeks. Olfactory function scores on the Sniffin' Sticks Test raised 33 % in those who received treatment (according to Konstantinidis et al., as cited in Miwa et al., 2019). As a side note, olfactory training has also been shown to enhance functioning in non-traumatic olfactory dysfunctions, such as those following viral infections (according to Hummel et al., as cited in Miwa et al., 2019). It is worth mentioning, that to date no medication has been scientifically shown beneficial in cases of viral olfactory impairments (Miwa et al., 2019).

In conclusion, olfactory training is a promising therapeutic treatment for olfactory loss. Although the effectiveness of olfactory training programs has been observed in several

groups of patients with anosmia and hyposmia, the neurological basis of the intervention remains poorly understood.

Measuring Olfaction

Olfaction is considered an especially challenging sense to measure as smells are invisible, unlike vision, and can only be perceived in a proximal environment, unlike sounds that can be heard by multiple people who are further apart. There are no official and/or universal clinical practice guidelines for the detection of olfactory dysfunctions (Miwa et al., 2019). There are, nonetheless, several measures designed to assess olfaction. Common olfactory assessments are here discussed.

Psychophysical techniques are a frequent component of olfactory assessments. The procedure consists of the presentation of different odors to a patient and the assessment of the respective response. Results are then adjusted according to age, sex, as well as clinical individualities. Psychophysical measures can be given in the form of odor differentiation, odor identification, magnitude estimation of odor intensities, odor detection threshold, or odor recognition memory tasks (Rombaux et al., 2009). Several olfactory tests consist of the verbal identification of odors from an array of descriptors. This simple and generally accessible method could, nonetheless, have the shortcoming of not being well suited for patients with impaired cognitive abilities or compromised awareness.

Among the most common orthonasal, i. e., through sniffing, olfactory measures lies the Sniffin' Sticks Identification Test (Hummel, Kobal, Gudziol, & Mackay-Sim, 2007). In this quantitative assessment patients are prompted to identify target odor(s), presented on felt-tip pens, from an array of different odorants. Odorants include cinnamon, apple, leather, fish, pineapple, sesame oil, etc. Odor threshold, odor discrimination, and odor identification are all part of the Sniffin' Sticks assessment. Together such measurements generate the "threshold-discrimination-identification" score that quantifies the patient's olfactory function. Retronasal Tests, on the other hand, reside on the assessment of olfaction at the back of the nasal cavity. This is done (a) through the mouth, e. g., with odorous powders applied to the tongue, or (b) via the nasal cavity itself — via canulas attached to an olfactometer (Rombaux et al., 2009). Similar to orthonasal identification, participants are asked to match the odor to an array of different smells (Ibid.).

Other reliable and valid measures are: the Scandinavian Odor-Identification Test, where sixteen odors are successively presented and the subject is given four possible responses per stimulus to choose from (Nordin, Brämerson, Liden, & Bende, 1998); the San Diego Odor Identification Test, consisting of eight common household odorants in an opaque jar (Krantz et al., 2009); the University of Pennsylvania Smell Identification Test (UPSIT) which can be self-administered and uses microencapsulated odorants accessed via the scratching of standardized impregnated test booklets (Doty, Shaman, Kimmelman, & Dann, 1984); a Brazilian-Portuguese version of the UPSIT is available

and could serve as an alternative for native Portuguese speakers (Silveira-Moriyama et al., 2010); there is also a shorter version of the UPSIT, the Brief Smell Identification Test (B-SIT), with 12 scratchable odorants (Krantz et al., 2009).

In an attempt to establish standardized olfactory assessment and treatment guidelines for clinical settings, the Japanese Rhinologic Society (JRS) founded the Subcommittee of the Japanese Clinical Practice Guideline. In Japan, olfactory dysfunction is commonly measured through the T&T olfactometer assessment. The T&T intravenous test is composed of five different odors (methyl cyclopentenolone, skatole, b-phenylethyl alcohol, g-undecalactone, and isovaleric acid) with seven or eight graded concentration levels. Odor detection and recognition thresholds are recorded generating a mean T&T score considering all odors, concentrations, and both nostrils where 1.0 or less is considered normal and 5.6 or higher categorized as anosmia (Miwa et al., 2019). Another olfactory test commonly administered in Japan is the intravenous injection of thiamine Propyldisulfide (Alinamin), a substance characterized by a garlic-like odor sensation. This subjective assessment captures the mean latency time and duration of such sensation with 8 s and 70 s, respectively, considered healthy. Prognosis has been found to be significantly worse in subjects who do not respond to Alinamin (Ibid.).

Olfactory Event Related Potentials (ERPs) is a technique to measure the brain's response to a stimulus in a person's environment. An olfactometer delivers the odor through either a "flow" or a "pulse" method which induces polyphasic response signals (Martin, 2013; Rombaux et al., 2009). The continuous odor flow is considered a superior technique to measure odor-evoked ERPs (Martin, 2013). Chemosensory ERPs generally confirm the results of psychophysical olfactory tests (Rombaux et al., 2009). It is important for the chemosensory stimuli to be presented repetitively with a steep onset (Ibid.).

Unlike the most common olfactory assessment techniques described above, Pistoia et al. (2015) used an olfactory imagination task to investigate uncovered consciousness. The studied patient had severe brain injuries and was initially considered mostly cognitively unaware. The subject was prompted to think about an unpleasant odor. The subsequently induced EEG patterns indicated that the participant was indeed consciously aware as their brain promptly responded to the delivered task. Pistoia et al. (2015) innovatively suggested that (a) olfactory imagination is more available to the injured brain than other non-olfactory stimuli, and (b) that olfactory imagination, without the presence of the actual smell, can indicate conscious awareness.

Lurian and Neolurian Neurofunctional Paradigms

The *Neuropsychological Factor* concept, coined by A. R. Luria, refers to the neurological impairment of a local brain region and its corresponding psychological expression (Luria, 1973). The concept stresses the importance of qualitative and comprehensive assessments of somatic and psychological symptoms in determining the location of the brain damage responsible for an observed abnormality (Peña-Casanova & Sigg-Alonso, 2020).

A. R. Luria recognized that mental activities rely on the collective functioning of distinct neurological regions. The neuroscientist further identified three main

functional areas within the brain, each responsible for a cluster of capacities. According to Luria (1973), the first subregion composed of the brain stem, diencephalon, and mesial portions of the cortex is involved in *regulating tone and waking and mental states*. Parolfactory regions, olfactory bulbs, and the hippocampus can be found in this region. The second subregion, i. e., lateral postcentral regions of the neocortex on the convex surface of the hemispheres, is important for *obtaining, processing and storing information coming from the outside world*. Olfactory structures within the second unit are the primary olfactory cortex and parolfactory regions. Lastly, the precentral anterior regions of the hemispheres are responsible for *programming, regulating and verifying mental activity* (Luria, 1973) with the integration of cortical and subcortical systems.

Peña-Casanova (2018) further developed on the three subunits initially proposed by Luria advocating for a total of five modified functional subregions within the brain. The two added regions were (a) striatal (basal ganglia) systems (unit IV) and (b) cerebellar structures (unit V). Peña-Casanova's model differs from Luria's in that it (1) includes aspects not incorporated in the three-regions model and (2) is not cortico-centric with a greater focus around the subcortex. Luria's perception of the brain as a complex functional system with distinctive collaborative regions persists in the five-unit model. Through the addition of units IV and V, Peña-Casanova (2018) covers important subcortical regions involved in olfaction. The olfactory tubercle, found in the limbic striatum (unit IV), is a strong respondent to presented odors. The structure is highly involved in odor motivated behaviors and reward cognition (Ashwell & Mai, 2012). Moreover, the addition of unit V speaks to the contemporary understanding of the cerebellum as a region involved in communication across cortical and subcortical regions. It is moreover believed that the cerebral unit V contains a feedback mechanism that responds to changing odor concentration (Sobel et al., 1998).

We will base ourselves on the first unit of Luria's concept to assess how capable a given patient is to receive olfactory information. Our goal is to achieve a more comprehensive clinical picture with insights around neurofunctional capacities. The fifth cerebral unit proposed by Peña-Casanova will also be a starting point for the development of our olfactory assessment tool; we plan to measure how patients with neuropsychological impairments respond to different odor concentrations.

Discussion and Future Directions

Our primary focus was on olfaction. This sensory function is empirically supported to distinguishably influence neuropsychological domains. Held in the most archaic regions of the brain, known as the rhinencephalon, olfaction is a unique sense in which perception takes place, mostly, bypassing the thalamus. The rudimentary rhinencephalon has few connections to brain zones that, from an evolutionary point of view, have more recent origins, such as the neocortex where the centers of language are found (Scliar, 2020). The, comparably, direct pathway involved in smelling is believed to explain some of the unique

characteristics of the olfactory sense. Those include the great relationship between smell and emotions, and the often subconscious nature of the olfactory process which makes olfaction highly influential of how people function and experience their surroundings; olfaction can influence emotional and psychological states and is, thus, highly associated with the development of psychopathologies. The fact that smells can often be perceived by the brain without conscious awareness often allows it to be responsive in unconscious patients. This is an important consideration in the context of neuropsychological testing where patients are often unresponsive to cognitive assessments. The olfactory sense could serve as an alternative, and supplementary, tool to explore brain functioning in severely debilitated patients.

The empirical body of literature has linked olfactory dysfunctions to a wide-range of health conditions. Those include, but are not limited to, neurological and neurodegenerative illnesses, such as traumatic brain injuries, cerebrovascular accidents and Alzheimer's disease, Parkinson's Disease, psychological disorders, including anxiety, depression, and psychotic conditions, and even the current pandemic of SARS-CoV2 (e.g., Hornuss et al., 2020; Rottstaedt et al., 2018; Sun et al., 2012; Xiao et al., 2014). Assessing abnormalities in olfaction is, thus, crucial as it may help diagnose numerous conditions that affect the human brain. Notably, olfactory deficits often serve as biomarkers for conditions when they manifest themselves prior to other symptoms (Martin, 2013; Sun et al., 2012). Examining olfaction in patients who already have a pre-existing diagnosis can also be insightful given that olfactory abilities provide cues regarding the prognosis of several neuropsychological conditions. In other words, functional olfaction often indicates greater chances of successful rehabilitation (Callahan & Hinkebein, 2002). It is crucial for healthcare providers, clinical patients, and the general population alike to be vigilant to issues around olfaction. If those are experienced, they must be examined as a potential indicator of other health complications.

Neuropsychological testing is a central component of the diagnostic process for clinical conditions. The goal is to identify and differentiate illnesses, assess the severity of a disorder, understand the patient's daily experiences and limitations caused by the condition, as well as make prognostic estimations based on baseline impairment. The standardized Neuropsychological scales currently used by professionals of the field, such as the Glasgow Coma Scale (Teasdale & Jennett, 1976) and The Mini-Mental State Examination (Martin, 1990), are largely focused on cognitive domains. While they evaluate the superior mental functions such as, attention, learning, memory, and other executive and motor functions, they leave sensory capacities behind. We argue that including sensory scales to the neuropsychological assessment battery would provide a more thorough and comprehensive understanding of a patient's health and well-being as well as allow for more informed and timely diagnosis.

We decided to begin by developing an olfactory battery suited to be included in neuropsychological assessments. We will base ourselves on the first unit of Luria's concept to assess how capable a given patient is to receive olfactory information. This could be fundamental for patients who are particularly compromised in their cognitive

capacities and would, thus, likely not be responsive to standard neuropsychological tests that require greater cognizance levels. Luria described his first unit as one responsible for *regulating tone and waking and mental states*. In accordance with the research previously described, parolfactory regions and olfactory bulbs can be found in this region, which once again highlights the tight relations between olfaction and conscious neurological states. Through the measurement of patients' responses to an array of selected odors, we hope to contribute to a more comprehensive clinical picture and to a better understanding of subconscious neurological functioning in those with severe cognitive impairments.

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