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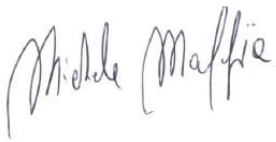

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The role of Autophagy in Hepatocellular Carcinoma

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Abstract

Autophagy is a cellular catabolic process in which cytoplasmic material is delivered to lysosomes for degradation. The autophagy process is regulated by highly conserved autophagy-related genes (ATGs) via different signalling pathways. Among the various biological functions of autophagy, the link between autophagy and cancer has been extensively studied, demonstrating its dual role, of tumor suppressor or promoter in cancer development. Hepatocellular carcinoma (HCC) is one of the most lethal cancers that affects most of the world's population and it is caused by different etiological factors: HBV and HCV viral infections, heavy alcohol consumption, NAFLD (non-alcoholic fatty liver disease), aflatoxin B1 contaminated food. In recent years, the involvement of autophagy in both prevention and promotion of liver cancer has been increasingly studied. Here, we summarize molecular mechanisms and physiological function of liver autophagy, its dual role and its therapeutic potential in HCC.

Keywords: Hepatocellular carcinoma, autophagy

I. Introduction

The word Autophagy derives from the Greek roots "auto"(self) and "phagy" (eating) and was described for the first time by Cristian De Duve in the 1963 (Ravikumar, Sarkar et al. 2010).

Autophagy is a cellular catabolic process in which cytoplasmic material is delivered to the lysosome for degradation.

Intracellular components must be recycled to maintain energy and to ensure quality control of proteins and organelles, thus allowing cells to control homeostasis (Klionsky and Emr 2000, Klionsky 2007). Several types of factors including low ATP levels, nutrient and growth factor deficiency, hypoxic conditions, endoplasmic reticulum (ER) stress, pathogen entry or anticancer drugs may further upregulated autophagy (Yang and Klionsky 2010). In light of the multiple ways by which autophagy participates in the control of cell homeostasis, it is no surprise to observe alterations of this process concerning the pathogenesis of different diseases, such as neural degeneration, inflammatory bowel disease, aging and cancer (Chen and Karantza 2011). The latter scenario has been extensively studied (Kondo, Kanzawa et al. 2005, Jin and White 2007, Mathew, Karantza-Wadsworth et al. 2007, Eskelinen 2011, Rubinsztein, Codogno et al. 2012, Wu, Coffelt et al. 2012), demonstrating the dual role of autophagy in cancer development. Autophagy can act as tumour suppressor by i) inhibition of inflammation, ii) prevention of p62/SQSTM1(sequestosome 1) accumulation and iii) promotion of genomic stability. On the other hand, autophagy can promote cancer cell survival, protecting cancer cells from different cellular stress responses, including starvation, oxidative stress and DNA damage(White and DiPaola 2009).

Hepatocellular carcinoma (HCC) is one of the most common primary liver malignancy and a leading cause of cancer-related death worldwide (Liu, Liao et al. 2017). Currently, surgical resection is recommended for very early stage and early stage of HCC, following

chemo/radiotherapy. However, these approaches are limited and not curative. HCC recurrence and metastasis are observed after surgery (He, Lei et al. 2012, Ma, Wang et al. 2015, Sheng, Qin et al. 2018). Therefore, the understanding of precise contributions of deregulated molecular and cellular alterations it is essential to delineate the mechanism of tumorigenesis.

The most prominent aetiological factors associated with HCC development are: i)chronic hepatitis B (HBV) and C (HCV) viral infections; ii) chronic alcohol consumption and iii) aflatoxin B1 contaminated food (Liu, Liao et al. 2017). Besides, non-alcoholic and alcoholic fatty liver disease both contribute to the development of HCC.

Based on different studies autophagy appears to have a significant role in hepatocellular carcinogenesis. This suggestion is supported by the observations that autophagy is either involved in HCC promotion or prevention. This means that the overall functional effect on cancer pathology is likely to be dependent on multiple factors that may also influence dynamically the proposed autophagy-cancer model (Shintani and Klionsky 2004, White and DiPaola 2009, White 2015). Autophagy allows carcinoma cells to survive in the tumor microenvironment under stress condition including chemotherapies. On the other hand, it suppresses tumor initiation in healthy liver by ensuring the normal function of cells. Unfortunately, the exact mechanisms of autophagy regulation, in hetapocarcinogenesis, are not fully understood until now.

In this review, we present a brief overview of molecular mechanisms and physiological functions of autophagy. Moreover, we highlight recent data that describe the dual role of autophagy in HCC. Therapeutic approaches aimed at modulating autophagy are also discussed.

II. Mechanism and physiological role of autophagy

Autophagy process consists of three main steps: *initiation, elongation, maturation and fusion* of a double-membrane vesicle called *phagosome*. These steps are regulated by a series of highly conserved autophagy related genes (ATGs) via different signalling pathways (Yang and Klionsky 2009). The process starts with the formation of a double membrane vesicle known as *auto-phagosome* that engulfed cytoplasmic molecules. The membrane sources for auto-phagosome formation are ER, mitochondria and plasma membrane. The initiation of the auto-phagosome is under the control of two macromolecular complexes: mTOR-Atg13-ULK1 complex that initiates the generation of the two isolated membranes which extend to form phagophore, and PI3K complex (composed of Beclin1, Vps34, p150, Ambra1, UVRAG) that instead recruits the subsequent ATG proteins onto phagophore membrane(Liu, Liao et al. 2017).

The second step is characterized by the elongation of the auto-phagosome. This process involves two ubiquitin like conjugation systems, Atg5-Atg12 conjugation and LC3 phosphatidylethanolamine (PE) conjugation.

In the maturation step, auto-phagosomes that in mammalian are formed randomly in the cytoplasm, move bidirectionally along microtubules, preferentially towards the microtubule organization center (MTOC), where the lysosome are enriched. Auto-phagosome first fuse with endosomes and then with lysosome where the sequestered contents undergo degradation. The fusion machinery is recruited on the auto-phagosomes thanks to UVRAG and Beclin1 interacting proteins (Parzych and Klionsky 2014). In this way, the degradation products of cytoplasm portions will be cycled for energy generating and substrate supplying (Glick, Barth et al. 2010).

In the last years, considerable data have been accumulated about the physiological role of autophagy in the liver e.g. clearing misfolded proteins, regulation of nutrient and energy metabolism in hepatocytes, selective organelle degradation, and lipid and alcohol metabolism. Autophagy alterations may likely have a significant functional impact on all these processes.

Autophagy in clearing misfolded proteins

Autophagy together with the ubiquitin proteasome systems is involved in the control of intracellular protein homeostasis (Marfany, Farràs et al. 2008, Knævelsrud and Simonsen 2010). Piece of evidence from *Atg7* gene deficient mice showed accumulation of polyubiquitinated proteins and deformed mitochondria, as

well as an increasing number of peroxisomes and lipid droplets in hepatocytes (Komatsu, Waguri et al. 2005). Furthermore, *Atg7* deficient mice developed hepatomegaly and hepatic failure, thus suggesting the important role of autophagy in liver metabolism (Komatsu, Waguri et al. 2005).
Similar effects were also observed after the loss of *Vps34*, a gene that is essential in the autophagosome formation (Jaber, Dou et al. 2012).
Recent studies have provided evidence that autophagy may play a fundamental role in the degradation of alpha-1-antitrypsin (ATZ) that causes protein misfolding, pulmonary emphysema, chronic liver inflammation and HCC (Kamimoto, Shoji et al. 2006, Perlmutter 2006).
Until now, remains unclear how autophagy recognizes and removes the misfolded proteins, even though a recent study suggests the involvement of the UPR (unfolding protein response) pathway (Ding and Yin 2008).

Autophagy in organelle degradation

Autophagy is involved in organelle sequestration and turnover in hepatocytes. During autophagy process, the degradation rate of mitochondria, endoplasmic reticulum, membranes, ribosomes and Golgi apparatus is different from each other, thus indicating a specificity and selectivity of the autophagy process in various cellular constituents. Indeed, the two terms "mitophagy" and "ERphagy" were coined to imply the two selective processes in removing the mitochondria and ER. The exact molecular mechanism for mitophagy in liver cells remains to be further clarified, but it is clear that autophagy disruption causes mitochondrial dysfunction with a consequent increase in the reactive oxygen species (ROS) generation and DNA damage (Kim, Rodriguez-Enriquez et al. 2007).
The first evidence of ERphagy was established with the observation that extra smooth ER membranes could be degraded by autophagic vesicles selectively (Kanai, Watanabe et al. 1993).

Autophagy and nutrient stress

The most important and efficient inducer of autophagy is nutrient stress. In animal liver, starvation causes the largest proportion of protein loss (Addis, Poo et al. 1936), that determines a transient increase in the aminoacid levels in the liver tissue and blood after 24h in wild type mice but not in *Atg7* deficient mice. Aminoacids supplied during autophagy can be used for energy providing by means the tricarboxylic acid cycle (TCA) thus contributing to the metabolic requirements of cells. This data highlights the important role of autophagy in protein degradation in the liver. Similarly, the glucose level in the blood was stable after 24h of starvation in wild type mice, while *Atg7* deficient mice displayed hypoglycaemia (Ezaki, Matsumoto et al. 2011). Under starvation, free fatty acids in the liver can be esterified into triglycerides in lipid droplets which will be selectively degraded by autophagy to supply energy production through β-oxidation (Singh, Kaushik et al. 2009, Kaushik, Rodriguez-Navarro et al. 2011).
The suppression of autophagy in *Atg7* deficient mice shows accumulation of triglycerides and cholesterols in lipid droplets, thus indicating an important role in lipolysis blocking (Singh, Kaushik et al. 2009).

Autophagy and energy metabolism

It is well established that autophagy process is ATP dependent and depletion of ATP will impair autophagy. Under energy-low conditions including starvation, the energy sensor AMP-activated protein kinase (AMPK) acts as a metabolic checkpoint in inhibiting cellular growth and promoting autophagy (Hardie 2011).
AMPK can activate autophagy by at least two mechanisms: through the activation of ULK1, and through the inhibition of the suppressive effect of mTORC1 (Mihaylova and Shaw 2011).
Furthermore, it has been demonstrated that AICAR an analogue of AMP (adenosine monophosphate), suppressed autophagic sequestration of lactose dehydrogenase in hepatocytes, thus indicating the energy level is critical for autophagy regulation in the liver (Samari and Seglen 1998).

III. Implication of Autophagy in Hepatocarcinogenesis

The neoplastic evolution of HCC proceeds through a multi-step histological process that is less well defined with respect to other cancer

types. Various risk factors are involved in the HCC onset including:

- chronic hepatitis B and C viral infections;
- heavy alcohol consumption;
- ingestion of aflatoxin B1;
- NAFLD (non-alcoholic fatty liver disease);
- diabetes;
- obesity;
- genetic disorders such as hemochromatosis.

These different HCC-inducing aetiologies provoke continuous round of hepatocyte damage and regeneration, thus causing chronic liver disease.

The first step towards HCC is the formation of *hyperplastic nodules* of regenerating hepatocytes that have normal cytological features. Then these lesions can progress to *pre-malignant dysplastic nodules,* which have abnormal cytological features including clear cell changes and nuclear crowding. *Pre-malignant dysplastic nodules* may evolve to HCC that is able to invade the surrounding fibrous stroma and vessels and occasionally has metastatic potential.

The molecular analysis of human HCC has shown many genetic and epigenetic alterations that result in the deregulation of key oncogenes and tumor suppressor genes including: TP53, β-catenin, Erb, hepatocyte growth factor receptor (MET) and its ligand hepatocyte growth factor (HGF), p16, E-cadherin and cytochrome c oxidase subunit II (COX2). As a result, HCC arises from a unique combination of somatic genetic alterations in various signalling pathways that cooperate to promote oncogenesis.

Recently, an increasing number of reports have highlighted the interaction of autophagy with these pathways and its dual role in the carcinogenesis, inhibiting the initiation process, while promoting tumor growth, metastasis and therapeutic resistance during tumor progression (Fig.1).

Protective effect of Autophagy in Hepatocellular carcinoma initiation

Several lines of evidence suggest that autophagy protects against tumor initiation by maintaining intracellular homeostasis. *Atg* genes play a critical role in the induction of autophagy. The deletion of *Beclin1*, *Atg5* and *Atg7* were found to be associated with spontaneous tumorigenesis (Qu, Yu et al. 2003, Komatsu , Waguri et al. 2005, Takamura, Komatsu et al. 2011). The first link between autophagy and cancer development was established with the finding that *Beclin1* inhibits tumorigenesis (Liang, Jackson et al. 2000, Takamura, Komatsu et al. 2011). In fact, it has been shown that the frequency of spontaneous malignancies increases in *Beclin1* $^{+/-}$ mutant, where this mutation accelerate the development of HBV induced pre-malignant injury, together with increased cell proliferation and reduced autophagy *in vivo* (Qu, Yu et al. 2003).

Also, a mouse model with *Atg5* deletion demonstrated the development of liver adenomas, suggesting a tumor suppressive function of autophagy (Takamura, Komatsu et al. 2011). Furthermore, hepatic tumor cells showed swollen mitochondrial, oxidative stress and genomic damage responses. Similarly, *Atg7* $^{-/-}$ deficient mice displayed the same phenotype with the development of liver tumors (Takamura, Komatsu et al. 2011).

The deletion of *Atg5, Atg7* and *Beclin1* leads to accumulation of p62 resulting in the development of hepatocellular carcinoma (Ichimura, Kumanomidou et al. 2008). P62 is an autophagic substrate that is used in measuring autophagic activity. Its knockdown inhibits growth and proliferation. Moreover, autophagy deficiency increases damaged mitochondria accumulation, oxidative stress and deficiency in DNA repair which lead to chronic tissue damage and genome mutations in HPCs (hepatic progenitor cells), two key factors of oncogenesis.

Autophagy has been suggested to prevent cancer progression by suppression of inflammation. This was first observed in autophagic deficient mice showing elevated levels of inflammosome associated IL-1β and IL-18 cytokine production compared to wild type control (Saitoh, Fujita et al. 2008). Autophagy suppression was also associated with high levels of CXCL17 that promotes cell proliferation and migration. Its silencing induces autophagy thanks to the nuclear translocation of liver kinase B1 (LKB1) that phosphorylates and activates AMPK, resulting in the reduction of tumor volume and proliferation (Wang, Li et al. 2019).

Moreover, the protective effect of autophagy involved enhanced degradation of yes associated protein 1 (YAP), the major nuclear effector of the Hippo pathway that controls liver growth and YAP overexpression (Perra, Kowalik et al. 2014, Lee, Noon et al. 2018). YAP has been identified as an autophagy substrate and as an essential downstream mediator of tissue remodelling, progenitor cell activation and hepatocarcinogenesis in autophagy deficient liver. Indeed, mice with *Atg7* deficiency displayed increased YAP protein levels and overexpression of YAP target genes that drives hepatocyte proliferation leading to gross hepatomegaly. The deletion of YAP in *Atg7*$^{-/-}$animal model reduces HCC incidence. Therefore, autophagy, by controlling the degradation of YAP, acts as a gatekeeper of hepatic differentiation, growth regulation and carcinogenesis(Lee, Noon et al. 2018).

Autophagy has also been shown to contribute to the anti-proliferative activity of interferon gamma (INF-γ) that exerts anti-viral and anti-proliferative effects in cancer cells. Its inhibitory effects are abolished when autophagy is inhibited (Li, Du et al. 2012).

Autophagy can also be modulated by microRNA (miRNA). HCC multiple miRNAs that target autophagic genes can influence tumor growth.(Zhu, Wu et al. 2009, Frankel, Wen et al. 2011, Chang, Yan et al. 2012). For instance, miR-7 is a short non-coding molecule with a well-known tumor suppressive role in different cancer types. In HCC, miR-7 levels are significantly downregulated compared to normal samples. A forced increase of miR-7, causes an increase in autophagic activity by targeting the mTOR pathway. Overall, this leads to a decrease in cancer cell proliferation (Wang, Wang et al. 2017).

miR-85 is an essential component in liver tumor development, acting as tumor suppressor. In HCC cell line HepG2, miR-85 upregulates autophagy activity with a functional effect on cell cycle arrest(Zhou, Liu et al. 2017).

LncRNA PTEN1 (long non-coding RNA-PTEN1), a pseudogene of the tumor suppressor gene PTEN, induces autophagy as a pro-death response to suppress hepatocellular carcinoma (Chen, Tseng et al. 2015). LncRNA PTEN1 prevents the interaction of different miRNA with PTEN that in this way can inhibit the activation of PI3K/AKT pathway, thus inducing pro-death autophagy, resulting in the HCC cells death (Tay, Kats et al. 2011).

All these lines of evidence elucidate that autophagy mediates anti-tumor effects and participates in various signalling pathways directly or indirectly to prevent the onset and progression of hepatocellular carcinoma.

Autophagy as a pro-cancer mechanism in liver cancer

To date, important insights associate the activation of autophagy with several stress responses including starvation, growth factor deprivation, hypoxia, damaging stimuli and therapeutic agents. The overall functional effect in cancer cells, including HCC, is the activation of a pro-survival mechanism(Chen, Tseng et al. 2015). For example, basal autophagy is elevated in hypoxic regions of some tumor types, where plays an essential role in tumor cell survival. In fact, tumor neovascularization may not result in a homogenous vessels network, especially in the fast-growing tumor, where there are some regions within cancer cells depend on autophagy for their survival, due to the limited nutrients and oxygen (Degenhardt, Mathew et al. 2006). In hepatocyte and HCC, hypoxia induced autophagy through the stabilization of the transcriptional factor HIF (hypoxia inducible factor) that controls oxygen homoeostasis. In hypoxic conditions, the upregulation of HIFα induced autophagy by inhibiting the interaction between BCL-2 and Beclin1. This is due to the upregulation of Bcl-2/adenovirus E1B 19-kDa interacting protein 3 like (BNIP3) protein that by interacting with BCL-2 inhibits BCL-2/Beclin1 binding (Bellot, Garcia-Medina et al. 2009). Furthermore, hypoxia upregulates early growth response gene 1(Egr-1), a zinc finger nuclear protein that functions as a transcriptional regulator, that promotes migration in HCC cell lines (Sijtsema 1977). The first outcome of the hypoxic stress, is the extensive production of reactive oxygen species (ROS) that oxidize cellular components including DNA, lipids and proteins (Bjelland and Seeberg 2003, Scherz-Shouval and Elazar 2007). Tumors activate different mechanisms to eliminate intracellular ROS, like the upregulation of antioxidant protein NRF2 (Jain, Lamark et al. 2010). NRF2 is a cytoplasmic protein, that is

upregulated during autophagy, and translocates into the nucleus to regulate the transcription of different redox-balance proteins. Another way to control the excessive ROS production is by the removal of damaged organelles. Non-functional mitochondria represent the main source of ROS and the induction of mitophagy helps cell in the removing of these damage organelles, to maintain cell functions and bioenergetics(Lemasters 2005).

The analysis of 156 HCC patients has reported the presence of elevated levels of LC3-II (a key autophagic marker) and correlated this overexpression with clinical features including vascular invasion and lymph nodes metastasis. Moreover, the overexpression of LC3-II was also associated with an overall survival rate inferior of 5 years, thus suggesting autophagy involvement in the development and poor prognosis of HCC (Wu, Jia et al. 2014). Indeed, in HCC patients with advanced liver cancer, increased autophagy correlates with low survival rate (Lazova, Camp et al. 2012, Wu, Jia et al. 2014).

In HCC, miR-375 that is known to inhibit autophagy through the downregulation of ATG7, resulted to be under-expressed. Under hypoxic conditions, miR-375 suppressed the conversion of LC3-I in LC3-II thus blocking the autophagy flux, mitophagy in HCC cells and the elimination of damaged mitochondria to impaired viability of HCC cells.

These data suggested that autophagy promotes the survival of HCC cells under hypoxic condition in patients with a confirmed diagnosis of HCC.

In addition, autophagy is known to promote liver cancer development by inhibiting the expression of tumor suppressor (e.g. p53, p16, p21, and p27). As well, .it has been reported that the hypoxia induced autophagy contributes to the chemoresistence of HCC cells. Thus, blocking autophagy may be an ideal target for HCC. Some works have demonstrated the increased anti-cancer efficacy of Sorafenib (the only FDA approved therapy for HCC) when autophagy key genes like *BECN-1* and *ATG5* are inhibited. This data suggest that autophagy inhibitors may have a synergistic anti-tumor effect with chemotherapy (Yuan, Li et al. 2014).

Taken together, all these data support the idea that the pro- tumoral role of autophagy in hepatocarcinoma depend on the stages of the tumor development and that the inhibition of autophagy may be an anti-tumor mechanism in established HCC.

IV. Potential therapy targeting of autophagy in hepatocellular carcinoma

The potential therapeutic value of targeting autophagy in hepatocellular carcinoma arises from the consideration that autophagy is an accomplice of cancer cell survival under stress conditions. For this reason, autophagy inhibitors may enhance the sensitivity of cells to hypoxia and metabolic stress.

Several studies have demonstrated, in mouse model, that autophagy inhibition could enhance cell death by promoting the activation of tumor suppressor pathway. Autophagy inhibitors like 3-metyladednine (3-MA), which blocks the fusion between auto-phagosome and lysosome, can increase the effect of a meloxicam, a COX-2 selective drug, that has an anti-tumor effect in different tumors (Zhong, Dong et al. 2015). Similarly, Sorafenib, the earliest approved therapeutic drug for HCC patients with advanced stage of liver tumor, demonstrated an enhanced anti-tumor efficacy when autophagy is inhibited by Chloroquine (CQ), bafilomycin A1, or by a siRNA against *Beclin1* or *Atg5*. Sorafenif acts by targeting the RAF/MEK/ERK pathway, leading to the inhibition of tumor growth and neoangiogenesis (Wilhelm, Carter et al. 2004). However, it has been shown that Sorafenib is also able to induce autophagy both *in vitro* and *in vivo,* thus promoting survival of hepatocellular carcinoma*,* through an ERK/MAPK independent pathway (Shimizu, Takehara et al. 2012).

These different data suggest that the balance of the autophagy mechanism can be a way to overcome cellular resistance towards some antineoplastic treatments.

However, the physiological functions of autophagy are very important for normal cells and tissues. For this reason, an important question that remains open is whether a systemic autophagy defect affects only cancer growth or also normal tissue. Thus, several challenges will have to be addressed before testing autophagy modulating-approaches in clinical trials (Levine and Kroemer 2019). Firstly, it is necessary a better characterization of autophagy related

pathways in liver diseases; in particular, it should be consider that ATG genes can be involved in non-canonical autophagy pathway and that the manipulation of autophagy can interfere with other interconnected pathways. Secondly, it is very important to discover autophagy biomarkers to follow *in vivo*, for the development of autophagy-targeted strategies.
Thirdly, it is necessary to define a therapeutic time-window for chronic liver diseases, since type and level of autophagy changes during the progression of the disease. Finally, we need the development of strategies that target a specific type of cells in the liver, considering the important role of autophagy in all organs.
Therefore, all these aspects represent a great hotspot and a breakthrough point for reducing HCC risk and improving therapeutic efficacy.

V. Conclusions and future perspectives

Since the identification of the first ATG genes in yeast in 1990, significant efforts have been made in the understanding of molecular mechanisms driving autophagy. One of the emerging fields is the involvement of autophagy in cancer development. Among different kinds of cancer, HCC appears to be relevant to autophagy. In HCC, autophagy seems to play a dual role: it acts as tumor suppressor in the initial step of the disease, while promotes tumor development once HCC is well established. Therefore, different approaches are needed to modulate autophagy for liver cancer prevention and therapy. Although the high potential for autophagy modulation as a therapeutic method for HCC, the clinical application of these autophagy modulators remains unclear.
To summarize, future studies on the various functions of autophagy according to tumor stage, differentiation, and environmental and genetic factors are needed for the development of new treatment options for HCC patients.

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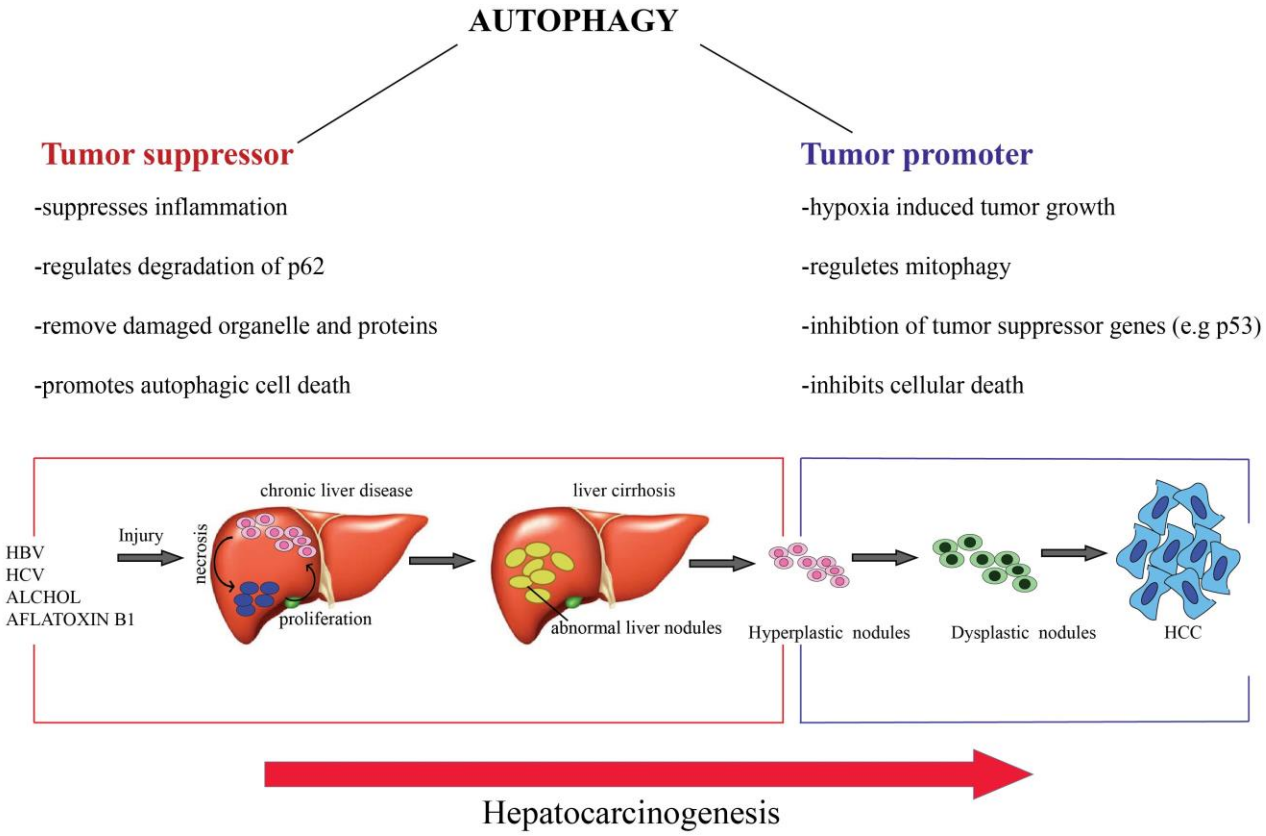

Figure 1: Dual role of autophagy in the initiation and development of hepatocellular carcinoma.
Hepatic autophagy is activated by various factors (HBV and HCV viral infections, heavy alcohol consumption, aflatoxin B1 contaminated food) that can cause hepatic injury after which there is necrosis followed by hepatocyte proliferation. Continuous cycles of this destructive–regenerative process promotes a chronic liver disease condition that culminates in liver cirrhosis. Subsequently, there is the formation of hyperplastic nodules, followed by dysplastic nodules and ultimately hepatocellular carcinoma (HCC) development.
By limiting inflammation, P62 accumulation, oxidative stress response and consequently inhibiting genomic instability, autophagy can serve as a tumor suppressor in the initiation stage of hepatocarcinogenesis. On the other hand, autophagy acts as a pro-survival mechanism to protect liver cancer cells against cell death induced by hypoxia, oxidative stress, starvation, DNA damage and therapeutic stress, thus promote liver cancer development

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An Augmented Reality Platform for Preoperative Surgical Planning

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Abstract
Researching in new technologies for diagnosis, planning and medical treatment have allowed the development of computer tools that provide new ways of representing data obtained from patient's medical images such as computed tomography (CT) and magnetic resonance imaging (MRI). In this sense, augmented reality (AR) technologies provide a new form of data representation by combining the common analysis using images and the ability to superimpose virtual 3D representations of the organs of the human body in the real environment. In this paper the development of a generic computer platform based on augmented reality technology for surgical preoperative planning is presented. In particular, the surgeon can navigate in the 3D models of the patient's organs in order to have the possibility to perfectly understand the anatomy and plan in the best way the surgical procedure. In addition, a touchless interaction with the virtual organs is available thanks to the use of an armband provided of electromiographic muscle sensors. To validate the system, we focused in a navigation through aorta artery for mitral valve repair surgery.

Keywords: Augmented reality, surgical planning, touchless interaction.

I. Introduction

Advances in computer technologies applied to medicine are offering new tools for diagnosis, preoperative planning, image-guided surgery, training and even the formulation of new treatments that help the surgeon to taking decisions before, during and after performing a surgical procedure. These advances are conferring considerable advantages on the patient, but they are also imposing an additional difficulty on the surgeon, who needs to develop new skills in order to adapt to newer systems (Lamata et al., 2010).
In this sense, the technology of augmented reality begins to be a novel alternative because it supposes in a single space a transition that combines common elements in the real world with virtual elements. In medicine, the use of the AR technology makes possible to overlay virtual models of the organs on the real patient; this allows the surgeon to have a sort of 'X-ray vision' of the patient's internal anatomy. AR 'augments' the surgeon's perception with a better spatial perception and a reduction of the duration of the surgical procedure (De Paolis and Ricciardi, 2018).
Thus, surgeons have at their disposal a mixture of techniques, between traditional and digital methods that involve new forms of representation, interaction and analysis of medical data.
Currently more and more research teams are approaching the world of augmented reality applied to medicine due to the necessity to refine surgical practices and reduce the human error factor alongside the specialist's experience with advanced techniques (De Paolis and Aloisio, 2018).
One of the first publications in this sense, presented by Wagner et al. (1995), consists of a visualization system for image-guided stereotactic navigation in tumour surgery that sought to provide an innovative tool using augmented reality instead of fully virtual environments. Some years later a research group from the University of Auvergne, began the development of a guided laparoscopy system in gynaecology (Collins et al., 2014). Subsequently, the original system was improved (Collins et al., 2016) involving a framework for the semi-automatic registering

of MRI images with the video of the laparoscopic procedure.
Another interesting works comprise specializations such as dental surgery (Wang et al., 2014), maxillo-facial surgery (Ricciardi, Copelli, De Paolis 2017; Ricciardi, Copelli, De Paolis, 2015), liver surgery (De Paolis, and Ricciardi 2018; De Paolis 2017) and neurosurgery (Kersten-Oerte et al., 2015; Indraccolo and De Paolis 2017)
In this paper a generic augmented reality platform for the manipulation of medical images (CT or MRI) and the visualization of anatomical structures in three dimensions is presented. The general concept of the system is to show the user an augmented scene (view of the real world and virtual elements) so that it can have a better spatial and shape understanding of the anatomical structures that will be involved in a surgical procedure. Also, the system provides the surgeon with a way to plan trajectories or movements that can be executed during minimally invasive procedures.
The platform has been designed in order to permit surgeon to navigate in the 3D models of the patient's organs in order to have the possibility to perfectly understand the anatomy and plan in the best way the surgical procedure. During the navigation it is possible to visualize the virtual environment in the helmet and also in a computer screen in order to provide the surgeon the possibility to discuss with other colleagues on the specific clinical case. A touchless interaction with the virtual organs is available thanks to the use of an armband provided of electromiographic muscle sensors.
In the current version, the system is capable to manage two clinical cases, which correspond to two different applications, one in heart surgery and the other in neuro-surgery that served as a basis for testing the proposed platform.

II. Methodology

The system proposed in this paper consists of a set of blocks that execute tasks in real time to create an augmented scene. The architecture shown in figure 1 consists of three types of devices (sensors) that permit the user (a surgeon) to visualize the 3D models of the organs and interact with these.

- a Myo armband is used to recognize some user's gestures and provide the system with commands used to manipulate transformations of the virtual models (Myo);
- a set of stereo cameras used to obtain the view of the real environment where the subject is located;
- an Oculus Rift helmet used to define a reference be-tween the space of virtual models and the position of the user's head.

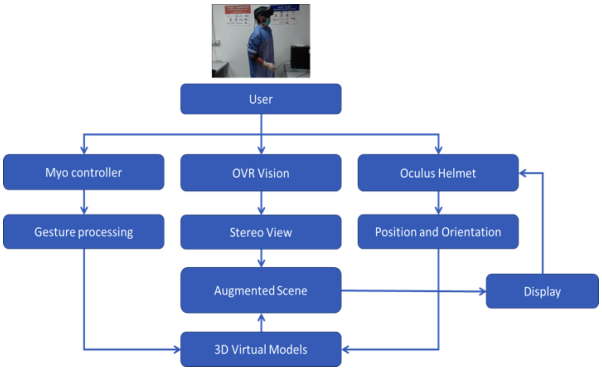

Figure 1. Architecture of the AR system

Additionally, the graphics device is responsible for duplicating the user's view of the RV helmet on a standard screen. From a functional point of view, AR application can be divided into three processing steps: tracking, alignment and rendering.
In the tracking step, Oculus OVRPlugin analyses the IR video data flow coming from the Oculus camera and processes the detected tracking system. Oculus's positional tracking system, used to track the position of the user's head, consisting of external infrared tracking sensors that optically track the headset. The Oculus is fitted with a series of infrared LEDs that permit to determine with sub-millimeter accuracy and near-zero latency the precise position of the device and, consequently, of the user's head.
During the alignment phase, some algorithms are used to align the virtual camera with the real one. This aims to make the portion of the augmented scene to appear perfectly coincident with the user's point of view that changes in real time. In every frame, the camera transformation matrix is calculated to consequently update the virtual objects parameters of position,

rotation and scale and make them proportional to the user's real movements.
In addition to this phase, it's necessary to consider a sub-phase that can be called "augmentation" of the Oculus point of view. This step consists into a second alignment phase to match the Oculus virtual camera with the ORVision virtual image plane, in which there is the video stream captured by the lenses of the stereo camera system attached on Oculus front cover. In this way, it's possible to convert a VR viewer, such as the Oculus Rift, into an immersive AR see-through system.
Finally, in the last phase of rendering, digital information is displayed in the augmented scene in such a way that the user hardly can distinguish the virtual objects from the real ones. For this purpose, some efficient graphics libraries and three-dimensional rendering engines are used to create the virtual elements, and moreover, to render the appropriate texture based on the virtual object.
Figure 2 shows the navigation and interaction system with all the involved devices:
1) Oculus tracking for virtual object positioning;
2) reference display of the model;
3) Myo armband for gestures detection;
4) Oculus Rift with the OVRVision Pro stereo camera.

Figure 2. Navigation and interaction system

III. Virtual Models

The reconstruction of virtual models has been made from CT images; two patient-specific cases were selected, a case of study for mitral valve surgery.
In the case of heart surgery the focus was the representation of the aorta, from the level of the groin to the heart, passing through the aortic valve to reach the mitral valve that empties into the left atrium.
The segmentation of the images was performed using semi-automatic algorithms based on thresholds, morphological operations (erosion and dilation) for noise reduction, elimination of islands and smoothing. Using the software 3D Slicer (3D Slicer), marching cubes algorithm was applied for the reconstruction of the surface of the segmented anatomical structures.
The resulting surfaces were submitted to post-processing using the MeshLab (Cignoni er al., 2008) software; later the models were refined and placed in their final position using Blender (Hess 2010) framework, where the experimental setup was built and later exported to Unity3D (Unity) engine.

IV. Gesture Recognition

The interaction with the virtual contents implements a touchless method through hand gestures and forearm movements. Myo armband uses electromiographic muscle sensors that, in contact with the skin, are able to read the electrical activity of the forearm muscles and to translate in real-time them into digital commands (Indraccolo and De Paolis 2017).
The association between the gestures and the tasks to be performed on the 3D models has been realized in such a way to implement a form of interaction as natural as possible as shown in Figure 3.

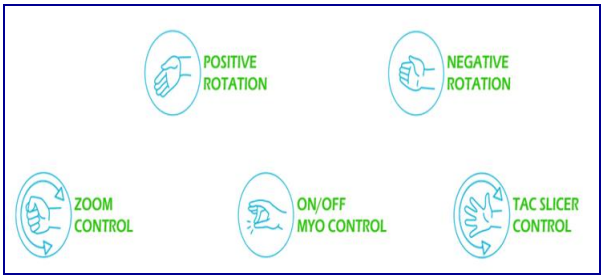

Figure 3. Recognized gestures and performed task

Two kinds of user feedback have been introduced to inform that the gesture has been detected and recognized: the first consists in a haptic feedback through a small vibration pattern inside Myo's hardware and the second one provides a graphic user interface on the top of the display device that allows to see if the Myo control is activated or deactivated. This is important because the surgeon can decide if the Myo controller must remain deactivated in order prevent incorrect or unwanted gestures.

V. Visualization System

Unity3D and Oculus Rift DK2 were used for the development of the visualization system.
The tracking system allows 6 degrees of freedom that are divided into rotational and positional tracking. The rotational tracking (with 1000 Hz refresh rate) is embedded inside the lenses using a gyroscope, an accelerometer and a magnetometer. For the positional tracking (with 60 Hz refresh rate) there is a camera with a near-infrared CMOS sensor that continually perceives the infrared points emitted by the HMD.
OVRVision Pro VR stereo camera were used to enable the augmented vision capability with the Oculus DK2, as shown in figure 4. The cameras were configured on full mode according to the manufacturer's description that adds a more realistic interaction. By means of the incorporation of the cameras on the scene of Unity it is possible to regulate the distance of each one of the cameras, as well as their vertical movement with respect to each other.

Figure 4. Oculus Rift and OVRVision Pro

VI. Conclusions

The surgeons showed great interest in the application of augmented reality and made suggestions for improvements and adaptations in other specialties. This is possible thanks to the general architecture of the system that allows the adaptation of new cases of study following the described methodology.
About the devices used, most of the users did not pre-sent problems to adapt to its use and managed to be-come familiar with the interface in short periods of time.
A variant of the system, that incorporates tracking using infrared technology, could be used to guide the surgeon during a procedure by superimposing the virtual models of the organs on the real patient; in this way the surgeon could have an increased view of the patient's anatomy and know in real time the position of the instrument inside the patient's body. That allows him to take more accurate decisions taking into account the anatomical structure of interest. However, this last task introduces some complications, such as the correct alignment of the virtual models with respect to the position of the patient in the operating room. Algorithms based on fiducial points are used in order to have a correct registration phase (Wagner et al., 1995). However, the use of pre-acquired CT images in order to obtain the 3D model of the organs is not possible if the surgery involves tissues that are deformed during the procedure; in that case is required the adoption of other algorithms able to adapt with precision the geometry obtained in the process of segmentation and reconstruction to the new situation in the patient's body.

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Postpartum Hemorrage: Are There Physiological Mechanisms of Prevention?

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Abstract
The postpartum hemorrhage (PPH) it is one of the worst complications of the pregnant woman and the leading cause of maternal mortality in the world, as it produces potentially catastrophic effects on patients, with high morbidity and morbidity. Likewise, the reduction in maternal mortality, which is particularly high in low income countries, but rising even in developed countries (as in USA), is one of the eight primary global health current goals of the WHO. In the complex pathophysiological phenomenon of PPH, the uterine contractility and connective tissue arrangement are poorly investigated. Both topics are scantly little understood and investigated, in terms of pelvic functional anatomy and pathophysiology. The anti-version uterine posture is essential for the optimal and necessary muscle contraction in the immediate postpartum stage, to avoid PPH onset. In this review, authors analyzed the physiology of uterine contraction related to the childbirth and the PPH, identifying an anatomical system involved in the physiological post-partum uterine contraction. This biological system is the integrated pelvic myofascial system and it has a prime importance in the physiological reduction of the PPH risk and to maintain uterine contractility during and after childbirth.

Keywords: Postpartum hemorrhage, uterine contraction, round ligaments, myofascial system, uterine posture.

1. Introduction

The postpartum hemorrhage (PPH) it is unfortunately a relatively widespread and common clinical condition; it is one of the main causes of severe maternal morbidity, causing 150,000 dead patients for year, that is, 25% of the 600,000 annual maternal deaths worldwide (Khan et al. 2006).
Unfortunately, basing on a study, approximately 3% to 5% of pregnants will experience PPH (Knight et al. 2009) and it causes, annually, one-fourth of maternal deaths worldwide (Say et al. 2014)
In developed nations, PPH has fallen to second or third place for direct maternal deaths behind hypertensive and thromboembolic complications (Khan et al. 2006; Knight et al. 2009; Say et al. 2014), while in high-income countries, 80 to 90% of maternal deaths from PPH may be avoidable for the delayed diagnosis and inadequate treatment (Fawcus 2019)
Beyond the direct consequences of acute hypovolemia, PPH exposes women to the complications of transfusion, resuscitation, infertility when treated by hysterectomy (1 case for 2000-3500 deliveries in developed countries), increased risks of thromboembolic complications, and greater psychological fragility (McNamara and Mallaiah 2019).
From the clinical point of view, the ACOG (American College of Obstetricians and Gynecologists) defines early PPH as at least 1,000 mL total blood loss, or loss of blood coinciding

with signs and symptoms of hypovolemia within 24 hours after delivery of the fetus or intrapartum loss ("ReVITALize Obstetric Data Definitions - ACOG" n.d.). Moreover, primary PPH may occur before delivery of the placenta and up to 24 hours after delivery of the fetus ("ReVITALize Obstetric Data Definitions - ACOG" n.d.).
PPH involves many hospital and university experts and specialists, is the subject of physiology and pathophysiology studies, stimulates pharmaceutical companies to seek new therapies and surgical instrumentation industries to produce devices to solve PPH.
In this review we will analyze the uterine physiology and the pathophysiology involving PPH, trying to evaluate the possibilities of physiological treatment in the resolution of the pathology.

2.1 Physiology of uterine contraction after delivery

Human anatomy is an extremely complex system tending towards semi-perfection, such as the intrinsic characteristics of the uterine muscle, on those of uterine contraction and on the unknown role that it carries out the whole myofascial system and the round ligaments.
The uterine muscle is a unitary smooth muscle differing from the multi-unit smooth muscle, because the contraction is synchronized by communicating junctions, that allow to coordinate the cells contraction (Egarter and Husslein 1992). The smooth muscle, despite having a myosin content of about 20% and a consumption of ATP 100 times lower than the skeletal muscle, can develop the same strength for transverse section area. It happens either for much slower rhythmical contractions, or for an architecture of the smooth muscle cell and the unitary organization of smooth muscle, structured in a syncytium (Egarter and Husslein 1992)
The uterine muscle behaves like a viscous mass and it is also characterized by a tension variability exerted at any given extent, and there is either no relationship between extent and tension, nor between extent and a length of rest (Sosa-Stanley and Peterson 2018)
Thanks to this plasticity, a strip of visceral smooth muscle, when stretched, first exerts a certain tension, but if the stretch is maintained, the tension gradually decreases and can go down to the initial or even lower level of tension (Sammali et al. 2018)
The uterine tone is a persistent state of partial contraction, showing continuous irregular contractions independent from the innervation and the membrane potential is unstable, with no real resting value (Roger Charles Young 2018)
The viscoelasticity of the uterine muscle is linked to the characteristics of the muscle fibers in the viscous component and to the collagen and elastin for the elastic component (Sammali et al. 2018)
The uterine muscle can, therefore, be considered as a "viscous mass" that needs to be oriented in extension and during contraction, with the lasting crucial role of the round ligaments (Sammali et al. 2018)

2.2 The anatomical role of round ligaments in uterine contractions

The round ligaments are formed by fibers and smooth muscles and, after the passage in the inguinal canals, by striated musculature (from the transversus and oblique abdominal muscles) (Chaudhry and Chaudhry 2019)
The round ligaments in the woman flap off in the labia majora and in the mountain of Venus (even in sexual activity the stimulation of these areas leads to uterine contractions of the orgasm) (Bellier et al. 2018)
The existence of the round ligaments, even if poorly represented, in quadrupeds, that obviously have the belly down and in which gravity favors the anterior position of the uterus, shows that they have more of a role of muscle-nerve terminal than of support (Iwanaga et al. 2016)
From a phylogenetic point of view, it is in women that the round ligament reaches its greatest development and it is not a vestige of the past (Iwanaga et al. 2016)
The round ligament is associated with the standing station and the new reproductive needs linked to this (Bulletti and De Ziegler 2006)
The need arises to anteriorize the uterus for abdominal development during pregnancy that would otherwise be suffocated in the pelvis or crush the large vessels, to make the cervix in the posterior fornix during coitus, but also because a uterus lying backwards in the postpar-

tum does not contract well (Sosa-Stanley and Peterson 2018; Sammali et al. 2018; Roger Charles Young 2018)
The round ligaments are improperly anatomically linked to the pelvic suspension system, because they are real muscles, as they can bear a load of 600 to 900 grams (Chaudhry and Chaudhry 2019)
Moreover, the round ligament is the essential element that determines the orientation of the body of the uterus "like a horse held by the reins" (Chaudhry and Chaudhry 2019)
During pregnancy, the round ligaments become 3 to 4 times thicker and the resistance they offer to traction increases up to 40 kg (Chaudhry and Chaudhry 2019) and, during pregnancy, they move away from the uterine fundus and the "Calza's Bundle" (central longitudinal band that in primates constitutes the neomyometrium of the uterus, not more bicorne as in the quadrupeds), from which they depart, is more anatomically evident (Kamina, P. Lorenzini 1975)
They orient uterine contraction surely also in labor and there are certainly different types of uterine contraction (Devedeux et al. 1993) with different receptors (or different sensitivity) for each muscular layer (neomyometrium, paleomyometrium and archimiometry) (Sosa-Stanley and Peterson 2018; Sammali et al. 2018; Roger Charles Young 2018)
Nevertheless, during Braxton Hicks contractions or in those in the latent phase of labor, in which the fetal head adapts to birth canal, they are probably not the same muscle fibers that contract in the active phase of labor (Maul et al. 2003) The round ligaments contractions could orient the uterus, adapting to its content and playing an important role during pregnancy and labor (Roger C. Young 2007)
The so called "ligament round pain", poorly diagnosed in Italy, is better known and investigated by Osteopaths than by the Obstetrician.

2.3 The hypothesis of integrated pelvic myofascial system

The uterine contraction in the expulsive stage of labor is "detrusor type" and leads to the fetal delivery. The uterine musculature, being in three layers, has the neo-myometrium (on the fund) that continues with the fibers of the round ligaments (like a Bolivian wool cap) (Escalante, NMM 2017)
In the postpartum uterine contraction, the uterine body is "guided" by the round ligaments, which contracts down and forward, and the lower uterine segment (LUS) contracts towards the pubic symphysis (Chaudhry and Chaudhry 2019)
All the studies on uterine contraction focused on the characteristics of the muscle fiber and on the electric potential of the membrane, rather than on the uterine muscle, structured in a syncytium (Devedeux et al. 1993).
Synthetic oxytocin stimulates the uterine fundal contraction, but not always the round ligaments or, at least, not at the same time and, hence, synthetic oxytocin cannot help the uterine posture (Maul et al. 2003; Roger C. Young 2007)
The first and second line standard pharmacological therapies for PPH, provided for by the national and international guidelines (Evensen, Anderson, and Fontaine 2017; Sentilhes et al. 2016) are less effective in all those situations in which there is an alteration of the myofascial system (obesity, supine position, cesarean section) that does not favor correct posture uterine during contraction (Vallera et al. 2017; Sentilhes et al. 2016)
Currently, in a mechanical-biological vision and with a more organicist anatomic-biological approach, mechanical forces must be considered together, and not only just into the uterine fibromuscular cell, typical of molecular biology.
Hence the hypothesis that the uterine contraction could depend not only by uterine muscle fibers, but by a complex integrated pelvic myofascial system, connecting the uterine muscle to the round ligaments, to the ileo-psoas muscles (via the genital femoral nerve) and to the muscles of the abdominal wall. The "axial fascia" or "deep fascia" (Bordoni and Simonelli 2018) wraps and connects the uterine muscle, its ligaments, the postural muscles in a single interconnected system, that, after delivery, progressively returns to the "status quo ante".
Currently, rethinking to obstetric daily experience in delivery room, it must therefore think to a rearrangement of the whole myofascial sys-

tem, favoring directly the abdominal viscera descent behind the uterus during labor and indirectly the in intra-abdominal pressure increase.
In the human body architecture, the myofascial system is the anatomical structure connects the anatomical districts and the human organs in the body (Bordoni and Simonelli 2018)
The term "fascia" refers to the collagen-fibrous tissues that are part of a broad system of transmission of tension forces in the human body (Bordoni 2019; Bordoni et al. 2018)
The "fascia" appears as an interconnected tension network consisting of the dense and loose connective tissue, from the surface to the depth. The ligaments are local densifications of this network. There is an extended continuity of the fibrous tissue, and the collagen tissue expresses a gradual transition. So, it is impossible to make a clear distinction between the ligament and the loose part of the intra-abdominal and pelvic fascia (Bordoni and Simonelli 2018; Bordoni 2019; Bordoni et al. 2018)
The fascial body therefore represents, within the human body, a wide anatomical structure with structural and functional network functions, consisting of bags, ropes (local densifications), thousands of cavities inside other cavities, all connected by robust or soft septa (Bordoni et al. 2019; Bordoni and Zanier 2014; Bordoni and Lagana 2019).
The "visceral fascia" consists of collagen and elastic fibers and covers the body cavities (Bordoni et al. 2019)
The bands wrapping the organs are called pleura, peritoneum, sheath, but they remain visceral bands (Bordoni and Simonelli 2018; Bordoni 2019; Bordoni et al. 2018, 2019). Very interesting is the significant increase in the risk of postpartum hemorrhage in Ehlers Danlos syndrome, characterized by severe connective tissue disorders.
In fact, pregnants with Ehlers Danlos syndrome experienced postpartum hemorrhage (19% vs. 7%) more often than the unaffected women (Lind and Wallenburg 2002)

3. Conclusions

There is a "global range" that, during pregnancy, is subject to mechanical tensions gradually increasing both from the growing fetus and from the pressures of the maternal uterus. The abdominal diaphragm has a sort of dome turned upside down. The pelvic diaphragm upwards and these two muscle groups are located at the upper and lower extremities of the peritoneal cavity which, like a balloon, encloses the abdominal organs. The transmission of pressure takes place inside (intra-abdominal) and outside (abdominal and trunk muscles) of this balloon and it is transmitted to all the abdominal organs, by an integrated pelvic myofascial system. This biological system should be adequately investigated for its fundamental importance in its ability to physiologically reduce the risk of PPH and to maintain uterine contractility during and after childbirth.

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Symbolic Universes: a specific declination within the Health Institution

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Abstract
The goal of this paper is to identify and interpret the relationship between the Symbolic Universes (S.U.) and their specific declination in the health context, more precisely how it is expressed in the focus groups on vaccinations. I will introduce to the reader the theoretical background that substantiates and motivates research. Starting from the adoption of the culturalist approach to psychological discipline, I will report the characteristics that distinguish it and the critical issues it tries to face. I will continue by illustrating the results of the first phase of the Re.Cri.Re. through the identification and definition of symbolic universes. I will then illustrate the methods and tools used to carry out research, the results obtained from the analysis and the interpretation of the results.

Keywords: cultural psychology; health institution, governance

1.0 Theorethical Background

1.1 Cultural psychology

Cultural psychology starts from the assumption that the human being gives meaning to what he encounters in the course of his life. Through this process of attribution of meaning, the human being does not just react or act on the basis of the surrounding environment, but builds the world with which he interacts and reacts. It differs from the rest of the psychology that prefers to look at the basic psychological functions (perception, attention), favoring the higher psychological functions that concern, instead, the voluntary construction of meanings. It is evident that this shift of attention (from something traditionally measurable such as behaviors, to something "less" measurable such as the processes of signification) involves the redefinition of the model, specific objectives and the privileged object of psychological discipline and function of the latter within the socio-cultural context.

1.2 The object of cultural psychology

Traditionally we believe that scientific knowledge is a stable and universal basis. If applied to psychological phenomena this definition is at least doubtful: how is it possible that the study of a transient, changing and subjective phenomenon can generate scientific knowledge? One of the solutions to this problem is, for example, to measure behavior. However, the problem arises again when the "observable part" of the behavior fails.

As mentioned, cultural psychology prefers higher psychological functions and, as we well know, at any time a social actor can consciously decide to act unexpectedly in a given situation. For this reason, "non-behavior" or the absence of behavior has the same value as "real" behavior. In other sciences (as in astrophysics) the absence of a phenomenon has the same value as the presence of the same phenomenon, both inserted in general development models.

For Valsiner, one of the problems of psychology was that of not being able to accept the "centrality of nothing, the lack" as part of something, of not being able to create its own model that was able to hold the elements together even when some of these were "missing", largely because it imposed the inductive generalization model instead of the abductive one as a form of empirical evidence:

The inductive path of generalization of knowledge requires the creation of categories of phenomena in which each instance is treated as

if it were an equivalent member of that class. (...) On the contrary, each person has their own unique story which is lost in such a generalization. (Valsiner, 2015).
Peirce developed this topic in his conception of the logic of scientific discovery, extending the meaning of abduction and considering it "the first step of scientific reasoning" in which a hypothesis is established to explain some empirical phenomena. For Peirce the human being has three different ways of inferring knowledge:

-Deductive reasoning
All the balls from that basket are white. (Implication report)
These balls come from that basket. (Antecedent)
These balls are white. (Result)
Deduction is a process in which the premises and rules are known and a conclusion is sought (ranging from general to particular). It starts from a general rule (implication relation), applies it to a specific (antecedent) fact and derives a certain (consequent) result. The conclusion will make explicit information that is present only implicitly in the premises.

-Inductive reasoning
These balls are white. (Antecedent)
These balls come from that basket. (Result)
All the balls in that basket are white. (Implication report)
Induction is a process in which the premises and the conclusion are known and the rules are to be reconstructed (from the particular to the general). It starts from a specific case (the antecedent), connects it to another fact (the consequent), and draws from it a probable general rule (implication relation)

-The abductive reasoning
These balls are white. (Result)
All the balls in that basket are white. (Implication report)
These balls come from that basket. (Antecedent)
Abduction is a process that is used when one knows the rules and the conclusion and wants to reconstruct the premises. It considers a specific fact (the consequent), connects it to a hypothetical rule (implication relationship) and derives an uncertain result, that is, a hypothetical conclusion (the antecedent).
About abduction, Peirce:
The form of inference, therefore, is this: The surprising fact, C, is observed; But if A were true, C would be a matter of course. Hence, there is reason to suspect that A is true." (Peirce, Harvard Lecture on Pragmatism, 1902/1976)
The use of inductive generalization in psychology increases the risk that the variability of the phenomenon is replaced by the "notion of score" (Valsiner, 2015) and that therefore the uniqueness of the phenomenon is lost. Why is it essential to protect the uniqueness of the phenomenon? As we have seen, the abductive reasoning aims to build the premises starting from the phenomenon through the connection of this to a hypothetical rule. Reducing the complexity of phenomena is one of the ways that psychology has used to respond to the needs of common sense, but this means losing the nature of the psychological phenomena that arise in the relationship between the world and the individual.
Negotiation is between the world and the individual (what Stern calls "the external infinity", that is, the imagination and knowledge of the world "and" the internal infinity, that is, the feeling of a person with respect to himself) of signs through their use. Considering a phenomenon like the product of this negotiation through a process of signification allows us to define precisely this dynamic of assigning meaning as the object of the discipline. All phenomena are subordinated to this process of signification. The behavior is therefore not objective but subjective, through the meanings linked to it. (Valsiner, 2017: 54). In this perspective, behavior is therefore the set of actions made significant by the human being.

1.3 The role of culture
For Valsiner people act through culture, inventing tools, signs and metasigns that organize the work done by other cultural tools. Culture is therefore located between ("in-between") the person and the social world and leaves its marks both on the environment and on the deep layers of the human soul.
The path that led culture to have a decisive role in psychological theory passes through Parsons'

studies which in '51 summarizes its fundamental characteristics: culture is transmitted (it is a social tradition), learned (not proper to the human being , not genetic) and shared. However, today these characteristics are no longer shared and have been replaced by others more suitable for the current model. Valsiner "overturns" the characteristics listed by Parsons: a culture that is transmitted, learned and shared is replaced by a co-constructed culture (through two-way communication processes, culture is co-built both between individuals of the same generation and between individuals of different generations), internalized / outsourced (messages are actively broken down and recomposed into new intrapsychic patterns and made available to other individuals), coordinated (the different social agents regulate the experience of their own vital worlds so that they can be mutually linked).
Culture is therefore constituted by the processes of construction and use that occur simultaneously in the intrapsychological and interpsychological fields. the subject builds significant relationships with the world first of all within his own subjective inner infinite while facing the environment perceived as meaningful in itself. (Valsiner, 2017: 72)
The fundamental role that here relies on culture in the symbolic mediation process places culture in-between: it catalyses the activity of signification of the individual and at the same time provides the frame within which meanings interact.

1.4 Meaning as a cultural model

The studies on the processes of signification carried out over the years clearly outline how the dynamics of creating meaning is a fundamental element to keep in mind when approaching the discipline. Before going into the study of signification processes, however, it is necessary to make some premises.
According to Salvatore, the traditional epistemological conception defines meaning as an autonomous entity, pre-existing to its public / private representation. According to this definition, individuals therefore have a given content in their mind (a concept, an image, a representation) and by virtue of this they can express it. However, this definition has undergone a series of revisions over the past thirty years due both to the increase in interest for some authors such as Wittgenstein and Peirce, and to the linguistic and semiotic turn of psychology. These innovations led to a pragmatic and contextual conception of the dynamics of signification which played a role of primary importance in the development of different areas of psychology.
"How strange it would be if logic were to deal with an ideal language and not ours. What should that ideal language express? Certainly what we express in our usual language; but then logic can only deal with this. Or it can deal with something else, but how can I simply know what it can be? Logical analysis is the analysis of something we have, not something we don't have. It will therefore be the analysis of propositions as they are ". (Wittgenstein, Philosophical observations, 2)
It is the assumption of ordinary language on the ground of logical analysis that gives rise to the important theory of "meaning as use", which constitutes the core of Philosophical Observations. In them, Wittgenstein writes that
"for a large class of cases even if not for all the cases in which we use them, the word meaning can be defined as follows: the meaning of a word is its use in language" (Wittgenstein, Philosophical observations, 2)
The importance of this theory is remarkable, and is linked to the principles that have proved extremely stimulating and fruitful. Wittgenstein downsizes the primacy of the structure or logical substance of language and the related logistical approach to it. He does not intend to affirm the "illogicality" of linguistic expressions, nor does he contest the existence of formal languages attributable to rigorous (formal) structures. His thesis is that there are types of linguistic communication which, far from being able or having to be evaluated primarily in the light of logical-formal criteria (objective and invariant), respond to needs, requirements and purposes to be analyzed in the light of criteria practical (not unique or universal). Secondly, Wittgenstein rehabilitates a somewhat pragmatic approach to linguistic reality: language is, for him, above all else, an interacting activity with the most disparate theoretical and practical-existential components of human life and doing (which Wittgenstein also calls the "lifestyle").
Understanding a linguistic expression therefore implies not so much the reference of it to cer-

tain pre-constituted essences or logical structures, but the understanding of the multiple factors (linguistic and extra-linguistic) cooperating in determining the meaning of this expression. From this point of view, tracing meaning back to use expresses the insertion of the linguistic phenomenon into a wider anthropological and socio-cultural context.
There is a psychology that designates meaning (and the dynamics of signification) as the fundamental object of the discipline.
"To consider a phenomenon as a process of signification means to conceive it as a dynamic of exchange of signs that allows distancing from the immediacy of experience. This semiotic vision offers itself as a general conceptual framework for modeling the set of phenomena generally associated with psychology". (Salvatore, 2015, 32)
The semiotic approach differs from the common sense vision of the meanings seen as static entities. A multitude of studies and developments of contemporary psychological thought that we can fit into the frame of socio-constructivism have highlighted the need to focus the analysis of psychological processes on the interpretative activity of individuals, a process within and by means of which the meaning it is co-constructed rather than merely applied. More precisely:
"Socio-constructivism has questioned the vision of meanings as fixed entities of the symbolic universe, opposing to it the idea according to which they do not pre-exist to the social and communicative exchange but are constructed and continuously redefined through and in function of this exchange "(Salvatore, 2015: 33)
It is therefore essential to provide the fundamental characteristics of the Sensemaking to make it easier to identify the ways in which this acts:

Contextuality: as we have already said, sensemaking is not an individual process, closed within the mind of the individual. On the contrary, it is an intrinsically social process that unfolds within and through the communicative exchange. Semantic structures must therefore be conceived as historical products, symbolic artifacts that the culture of a given social group configures and makes available to its members.

Situativeness: symbolic models do not pre-exist to communication and action but are properties emerging from these processes.

Pragmaticity: any act of thought is not a neutral act. The way in which individuals give meaning to experience is a social act animated by some intentionality, it is a fundamental lever through which they safeguard and mutually promote their expectations, versions of the world, systems of interests. (Salvatore, 2015: 34).

The absolute freedom of interpretation of the subject is therefore protected. Nonetheless, the recognition of the existence of the rest of the world is not questioned. Individuals do not "generate" the world, they make certain aspects pertinent, depending on how reality makes itself subject to be interpreted and experienced.

1.5 The performative value of the signification process
The process of signification is therefore not a particular or contingent process in communication / relationship but is understood here as a real object of analysis, the necessary prerequisite for it to be recognized as a theoretical object: an object that is therefore understood here as the whole of ways, connections and relationships that signs have over time. What has been said so far leads us to define the set of signs as a dynamic field of co-occurring elements that creates the conditions for its own reproduction. As we can see, this definition is similar to that developed by Maturana and Varela in the description of autopoietic systems: the meaning is therefore the general conformation, the scheme, which is created over time by the relationship between the elements and is therefore not only a specific component of the system.
The interpretative operation of the sign allows us to imagine a region of meaning that operates from a condition of interpretability, and it is in function of that area that therefore the sign is made pertinent. The relationship between the area of meaning and interpretation is not "upstream" of the interpretative act, but emerges precisely in the act, in the relationship between the signs within which the sign is inserted. The meaning is therefore performative, they establish the various areas that act as a condition of interpretability of the sign making them realities given.

In order to be "seen" and therefore subject to interpretation by the individual, the sign must necessarily be sensible: this means that there must be at least one "area of meaning" for which that sign has a meaning, an interpretative cast through the which sign can be recognized. It is worth now to deepen the concept of "area of sense" used so far: this is not declarative knowledge, it cannot be a direct object of experience, but it is a premise of sense activated contextually to the interpretative act of the sign that founds thought . To recall what was said in par. 1.2 is precisely this "absence", the semiotic cast that in this context assumes crucial importance. The object susceptible to experience therefore becomes an object of investment even when this object assumes critical and negative characteristics, determining a further characteristic of the dynamics of meaning, that is, which persists in its functioning regardless of the content of the representation.
Another characteristic of the dynamics of signification is its generalization. Once a sign has been made relevant, this "describes" the totality of the field of experience that was activated when the dynamic of signification was established. Various researches related to different social objects (Carli & Salvatore, 2001; Guidi & Salvatore, 2014; Manzo, Salvatore, Venuleo, Olive & Geusa, 2008; Mannarini, Ciavolino, Nitti & Salvatore, 2012; Pinto, Balestra, del Gottardo, Salvatore & Venuleo, 2008; Salvatore, Mannarini & Rubino 2004), have shown that the representation of specific objects is a function of the global image of the context conveyed by individuals. We can therefore infer that whenever a social practice calls for a generation of meaning, what we see is the totality of the field of experience active at the moment of the act of signification.

1.6 The affective component of the signification process

We find a psychodynamic component within the dynamics of signification in the field of affectivity: the meanings that substantiate the interpretation of the sign can be described as the product of a process of affective semiosis. The affects are basic forms of signification of the relationship with the world, definable as embodied general categories with hedonic value, within which the flow of experience is represented, divided and transformed into objects with relational quality (Carli and Paniccia, 1993). In the process of signification there is no pre-existing affective content which is then activated: the process consists rather of the continuous abductive construction of a particular area of meaning as a condition of interpretability of the experience.

1.7 The Re.Cri.Re Project

The Re.Cri.Re. Project aims to understand changes in social identity within the European community. It is designed to provide policy makers with a tool to plan intervention in different social contexts starting from the assumption that it is social identity that changes the impact and outcome that these interventions have on individuals.
As previously said, culture plays a fundamental role in the interpretation of social signs. The identification of different general, abstract, stable systems of meaning allows us to understand how individuals represent themselves and how they represent themselves in relation to the social environment: these systems of meaning are here called Symbolic Universes. Identifying the U.S. allows us to analyze which higher mental functions (see 1.1) are associated with the different symbolic universes and through which behavioral and communication forms are expressed in daily life and how the U.S. mediates the impact of political and social interventions in the social community.
As previously stated, the system of signification is semiopoietic and the development of the system is an endogenous process. To propose a system development means to favor a reorganization of the rules inside the system. Development cannot take place through the investment of resources capable of producing change since, in the world, development implies the production of resources. The abandonment of the regulatory approach of meanings does not mean that development is impossible: this implies the abandonment of meanings as "per se". Consequently, the development of the system will be oriented towards the management of semiotic dynamics, continuously implemented through the various social contingencies. Making the U.S. the goal of strategic interventions means developing a methodological approach that combines hermeneutic research aimed at understanding the anthropological and psycho-

logical aspects of cultural dynamics with a computational approach aimed at providing abstract mathematical models of their latent structure. This approach provides policy makers with a vision of the cultural milieu that allows assessing the impact of U.S. on social identity, but also to organize interventions and what consequences to expect from their implementation in social areas.

If we identified the signs as points within a semiotic space, the shift from one sign to the other can be interpreted as a shift within this space (Salvatore, 2016). This implies that the dynamics of signification can be understood as a trajectory of signs within a semiotic space. Borrowing the notion of "field" from physics which affirms that a field is a system whose internal organizational dynamics exerts an effect on the elements that constitute it, we can see how the definition of culture in terms of the field is a way to make the more general theory of signification dynamics which identifies the position of the subject as dependent on the semiotic space. From what has been said, we can see the U.S. as attractors active within the semiotic field that make a certain semiotic trajectory more likely than another. From a phenomenological point of view we can identify the activity of an attractor as a co-occurrence of ideas, habits, feelings, behaviors that tend to associate with each other and that determine the experience that the individual has of himself, of others, of the world. The internal organization of a field, therefore the salience of the attractors that characterize it, can be represented in terms of lines of force. A line of force describes the effect that local dynamics exerts on its elements due to their position within the field. Hence, a semiotic line of force detects the direction and magnitude of the effects to which the dynamic of individual signification is subjected, due to its position within the cultural milieu, once the latter is interpreted in terms of the semiotic field. Consequently, the variability of the individual trajectories of the dynamics of signification within a semiotic field can be seen as the manifestation of the interactions of semiotic lines of force. This means that each attractor of the semiotic field (therefore each U.S.) can be interpreted as the effect emerging from the interaction of certain semiotic lines of force.

As stated in 1.4 a semiotic line of force can be understood as an embodied dimension, full of affectivity. This is because, as has been said so far, the semiotic line of force detects the field dynamics: it is the constitutive element of the U.S., which outlines their ability to function as semantic attractors. The semiotic lines of force are therefore the core of the process of forming experience, highlight the two complementary semiotic processes through which this process unfolds: the process of pertinentisation of a part of the world that makes the phenomenon the object of experience and the attribution of an emotional charge to the relevant dimension of experience. it is important to underline how the qualities attributed to the relevant experience are modeled here in terms of antinomic structures (Good / Bad, Strong / Weak, Active / Passive). In this way it is possible to explain the bivalent dimension within which the meanings are articulated. The latent dimensions of sense act as semiotic lines of force with an oppositional structure: the semiotic activation of a certain quality is simultaneously the semiotic neutralization of the opposite quality. This means that moment by moment a particular state of semiotic trajectories emerges from a background composed of all potentially possible alternatives. The meaning of something therefore is not only given by the relationship "in presence", but also by the relations "in absence" between the signs (de Saussure 1916/1967; Salvatore, 2016; Salvatore, Tonti, Gennaro, 2017).

1.8 The Health Institution

For centuries, medicine has been a foregone institution of social control, a moral guardian of society with the power to discern between normality and deviance (Illich, 1976; Foucault, 1969; Parsons, 1951). The role of the patient was relegated to the passivity of a strong figure like the medical one; grateful and complacent with respect to taking charge of the indisputably benefactor, selfless and competent doctor (Porter, 2011).

In the last decades the medical role has undergone a strong weakening of the institutional legitimacy it has enjoyed for centuries. Today the health system must face new forms of demand, characterized not only by the request for a more efficient treatment, but also in terms of

improving personal performance and image. Furthermore, the easy accessibility of information on the web deludes people into believing that everyone can have a complete knowledge of themselves and this would allow them to manage their health not only without medical support, but also questioning the professionalism of the same (Brownstein et al., 2009; Hudak et al., 2009; Sommerhalder et al., 2009).

The erosion of the medical institution is visible from several aspects: An evident symptom of this is the increase in cases of burnout of doctors who are always subject to new requests and different stresses from the client / patient. Furthermore, it is expressed by the increase in the cost of medical insurance used to protect themselves from the legal consequences of the conflict with users. A third example is the increase in the number of incidents of violence and assault in hospitals and emergency rooms in the past few decades. For example, the estimated cost of violence and assault in new Hampshire exceeds £ 69 million per year (NHS Violence Towards NHS staff from the public, 2001).

On the one hand, these symptoms signal how patients developed agent conflict and on the other hand, they report that doctors are aware that the medical role has lost its institutional value which was previously mediated in form and content by the application. Through a modeling and methodological structure such as that which establishes the theoretical background of the Re.Cri.Re Project, we can interpret the results not at the content level but at a more abstract and general level which considers the content as the instantiation of the superordinate dynamics that organizes the culture in which the content is acted. This allows us to understand and analyze the erosion level of the medical institution: here the institution is seen as a system of meanings concerning a practice / social object that is deeply shared and homogeneous within the cultural milieu. The institution crystallizes a system of meanings that was initially developed by a certain social group in contingent circumstances and was reified / naturalized. It is so stable, invariant, indisputable and permanent, that it is experienced as a fact (Bergher & Luckmann, 1966). As said, the way of representing and acting the social object / practice becomes monolithic, non-negotiable, a piece of reality, transformed into a canonical order and taken for granted (Carli, 1982, Merleau-ponty, 1954). This definition clarifies how the erosion of the institution itself manifests itself in the plurality of meanings in which the object / practice is represented and acted on, new representations emerge, each of which is an expression of the reinterpretation of the object / practice in the light of a certain domain of meaning or value system which is rooted in the cultural milieu. Since these representations reflect different anchoring processes (Moscovici, 1976), each new representation has a content that can be more or less coherent with the system of meanings. For what has been said so far we can say that the cultural context of the medical role has an important effect on the perception of the same, in fact the symbolic power of the medical institution in the past was sufficient for the patient to be confident, receptive, assertive to the indications and requests of treatment and to assume that the indications could only be so, there was therefore no room for differences between individuals. Today, however, the medical institution in western society has experienced a fragmentation that also manifests itself with the loss of symbolic power and this also affects the vision of the health institution (Venezia, in press).

Therefore, the health demand was chosen as the object of analysis in light of the criticalities highlighted previously by processing the data with statistical tools in order to interpret the results through a semiotic approach that allows to investigate the latent dimensions of meaning that organize it.

1.9 The specific declination of Symbolic Universes

The purpose of this work is to highlight the relationship between the U.S. and their specific declination within some discussion groups on the topic of vaccinations. The choice of the theme is not accidental: although, as has been said so far, the relevance of each object of experience is the precipitate of some premises of meaning, a discussion on a "hot" topic such as that of vaccines, could favor the taking precise and defined positions within the focus group. The relationship between symbolic universes and specific object (health demand, vaccines) allows us to make explicit the links between the sense premises of individuals and how social

phenomena are experienced, and to policy-makers to point out targeted interventions with better expected outcomes.

2.0 Methods and research tools

2.1 V.O.C. Questionnaire

The tool used to identify the US is the VOC questionnaire (View of Context), a questionnaire consisting of 68 items that allows you to identify how individuals emotionally represent significant aspects of their lives and the world around them and how these representations are linked to their way of thinking and emotions. Through the statistical analysis (Multiple correspondence analysis, co-occurrence analysis, cluster analysis) five U.S. were identified:

Ordered Universe (O.U.)

Main features: sense of self-efficacy, perception of control over one's life, agency, sharing, altruism, respect for the rules, trust in others, cultural pluralism, trust in the future and in others.

The world is governed by an intrinsic order that fuels trust in the future and aversion to any form of opportunism, careerism, and abuse of power. Trust in the world and in others induces people to abandon selfish interest in favor of collective interest: sharing, solidarity and commitment are some of the values that inspire life in society. In this context, people can actively contribute to common well-being and this effort contributes to giving meaning to life.

At the same time, solidarity, sharing, trust and respect for others represent an individual development tool. Justice and morals are constitutive elements of the intrinsic order that governs the world where everyone can find his place.

Interpersonal Bond (I.B)

Main features: moderate perception of self-efficacy and control over the future, moderate trust in people, moderately optimistic vision, moderate trust in institutions, moderate investment in the future, moderate orientation towards inter-ethnic dialogue, moderate conformism. Personal fulfillment, adaptability, sharing, emotions.

The interpersonal ties, and the feelings of love and friendship that they convey, are what gives meaning to people's lives. They provide stability and protection and therefore justify the sacrifices that individuals make to keep them alive. In this perspective, conformism represents the most effective way to succeed in life in the face of a lack of openness towards diversity and a cautious optimism towards the future.

The relationship is what you should invest your time in: it conveys belonging and guarantees safety and development.

Caring Society (C.S)

Main features: trust in public institutions and organizations, positive view of the context, high perception of control, respect for the rules.

A full trust in society, its institutions and bodies, represents a secure basis that supports individual agency and the belief that the future holds only good things. Respect for the rules has priority over the needs and requirements of individuals who must be enslaved to the rules.

Trust in formal and social institutions ensures people well-being and nourishes hope for a better future. So what you need to do is respect the rules, express your needs and cultivate your passions.

Niche of belonging (N.B)

Main features: poor perception of control and interpersonal trust, pessimistic vision of the future and present, attribution to others or to the case of control over one's life, distrust of institutions, focus on the present, poor multicultural orientation, importance of emotional ties for which you can commit transgressions, shared values, economic interests, alliances with the strongest.

A moderate pessimism towards the future and the awareness of living in an anomic context greatly reduce the perception of control over one's life. Institutions and services are unreliable, especially law enforcement, the public administration and the health service. On the contrary, a more positive image characterizes institutions where there is more space for interpersonal relationships and social exchanges, such as school. The only way to "survive" and defend against external threats is by belonging to primary groups which constitute a solid foundation for identity.

Change can never be fully implemented. It is preferable to close oneself to novelties, not to adapt to them and maintain the status quo.

Other's World (O.W)

Main features: negative vision of the world, deep distrust of the future, devaluation of the context, fatalism, personalistic conception of power, no perception of control over one's life, following the current, little importance of feelings. Things are going badly and in the future they will be even worse. The world belongs to those who have power and use it unscrupulously. It is not possible to change things: people pursue selfish goals and do not count on each other. Institutions are not trustworthy, so what remains for people to do is to survive day after day, being on the side of the strongest, marrying their rules and point of view even at the cost of going against common morality. This is the only way to have a little control over your life. The lack of security, the instinct for survival, and fear make the world a violent place where corrupt power reigns in front of which one can not help but perceive a sense of helplessness and live day to day.

Following the administration of the questionnaire to the participants of the various focus groups, the symbolic universe was assigned to each participant, then reported in an Excel matrix and used as an illustrative variable in the interpretation of the results obtained from the analysis with T-Lab.

2.2 ACASM (Automatic analysis of co-occurrences for semantic mapping)

ACASM was recently developed (Salvatore et al., 2012) to overcome the limitations of traditional automated text analysis methods. ACASM is a bottom-up text analysis procedure based on explicit and invariant coding rules and yet capable of taking into account the contextuality of the meaning (Salvatore et al., 2012, p. 258).

ACASM aims to extrapolate thematic contents (for example semantic meanings) active in the text. Each thematic content is characterized by a cluster of words that tend to co-occur (that is, be associated with each other) in the text. Such sets of co-occurring words are identified by means of invariant rules but context-related through an ad-hoc software. ACASM belongs to the wider family of semantic analysis methods focused on the co-occurrence of lexical units (for example, ALCESTE, see Reinert, 1993; Latent Semantic Analysis [LSA], see Landauer & Dumais, 1997; Meaning Extraction method [MEM], see Chung & Pennebaker, 2008; see Wolf, Chung and Kordy,). Compared to most of these methods, the main specificity of ACASM is that it adopts as a context unit a single sentence or a group of a few sentences (the context unit is the text segment within which the co- occurrences). This context unit is smaller than that used by most other methods. This unit of context is chosen in order to make semantic analysis sensitive to the contingencies of communication, that is, how words tend to be combined with each other at a given limited time. The contingency of communication is an important component of contextual meaning (Salvatore, 2015). An initial ACASM validity study (Salvatore et al., 2012) was conducted in order to test the hypothesis that ACASM is functionally equivalent to a human bottom-up semantic analysis model based on common sense (Garfinkel, 1967; Valsiner, 2007). For this purpose, a validity criterion similar to that of the Turing test has been adopted, i.e. being able to consider ACASM as a valid semantic analysis method if and only if the analysis produced is indistinguishable from that produced by human interpreters (Salvatore et al., 2012, p.258). This criterion was adopted because in the case of bottom-up semantic analysis it is not possible to refer to an external, objective regulatory criterion on the basis of which the validity of the analysis can be assessed in absolute terms (Salvatore et al., 2012 , p 258). Thus, the performance of ACASM compared to a group of human interpreters (blind to the objectives of the study) were compared in relation to two specific semantic analysis tasks, namely the evaluation of the semantic similarity between different text units, and the bottom- up of a certain amount of these textual units, in clusters (ie thematic contents) based on their semantic meaning. The results showed that ACASM's performance is indistinguishable from that performed by human interpreters regarding these two tasks, thus providing empirical evidence of the validity of the semantic analysis performed by ACASM. The aforementioned study showed that ACASM is able to perform two semantic analysis operations (i.e., evaluation of the semantic similarity of text units and their bottom-up classification based on thematic content) in an indistinguishable way from human interpret-

ers, with the advantage of being more reliable and faster. ACASM is based on the theoretical and methodological framework illustrated in the first chapter: this implies the enhancement of abduction as a strategy for building knowledge in the field of psychosocial phenomena. The ACASM is based on the conception that meanings consist of a transition of signs: in the case of the text, the transition of the signs takes on forms of syntactic association i.e. co-occurrences between lexemes within the same contextual units (e.g. paragraph). The ACASM identifies the co-occurrences between lexemes by means of a multidimensional analysis procedure combining the correspondence analysis and cluster analysis applied to the corpus we treat. More specifically, the multidimensional procedure is applied to the data matrix thus composed: in line the segments into which the text is divided (e.g. paragraphs) and in column the lemmas. The cells indicate the presence or absence of the presence of the lemma in the segment. In general terms, the method allows to break down the entire lexical variability, that is the distribution of lemmas present in the text, in discrete units (factorial dimensions), corresponding to the behavior of one or more lemmas, or to a share of variability. Each factor identifies a structure of opposite subsets of co-occurrences of terms and can be represented geometrically as a spatial dimension - that is, an axis with two polarities. The words placed on the two different extreme polarities, can be considered most distant from each other. We conceptualize the dichotomous tension emerging between the two opposite patterns of words, in terms of an Active Symbolization Dimension within the emotional-cultural matrix expressed by the participants in the interview. In other words, the factors are interpreted as meaning structures, generative of the representational contents. Since factorial dimensions must be considered statistically independent of each other, the factors can be represented geometrically in terms of axes orthogonal to each other. This means that the combination of the n factors extracted from the analysis will produce a geometric space consisting of n descriptive dimensions, in good approximation, of the entire significance variability of the respondents. For this reason, we define this factorial space as a symbolic field.

The main analysis procedures applied to transcripts are described.

- Indexing
- Analysis of Lexical Correspondences (LCA)
- Cluster analysis (CA)

Indexing: The text, obtained from the complete transcription of the interviews, has been indexed to take into account the interviewee's illustrative variables. Indexing has been applied to the full transcription of the text. Lexical Correspondence Analysis (LCA): LCA is a factorial analysis procedure that works on nominal data (Benzecri, 1973). In general terms, the method allows to break down the entire lexical variability (i.e. the distribution of the lemmas present in the corpus) into discrete units, the factorial dimensions, corresponding to the behavior of one or more lemmas, or to a share of variability. Each factorial dimension identifies a structure of opposite subsets of co-occurrences of terms and is geometrically representable as a spatial dimension consisting of an axis with two polarities. The dichotomous tension between the two opposite patterns of words is interpreted as a sign of an active Symbolic Dimension within the emotional-cultural matrix expressed by the interviewees. The co-occurring words that characterize each factorial polarity concern aspects that do not have functional or semantic relationships; their aggregation, therefore, lends itself to be interpreted as the effect of a generalized meaning. Interpreting each dimension means understanding what common meaning emerges from the subset of terms that characterize a polarity and which from the subset of terms that characterize the other polarity, as well as understanding the second-order meaning that emerges from their aggregation.

The LCA allows you to identify a very large number of factors, each of which explains a decreasing share of inertia. In the present study we interpret the first two factorial dimensions, which correspond to the most significant Symbolic Dimensions identified through the interview. As statistically independent of each other, the factors can be represented geometrically in terms of axes orthogonal to each other. Conventionally the first factor is represented by the horizontal axis, the second by the vertical axis (figure 1). The two patterns of words making up each factor are defined by a label that identi-

fies a specific symbolization mode opposite to another mode, identifying the other pattern.
Cluster Analysis (AC): The AC is an analysis procedure aimed at identifying groupings of context units that share a certain number of co-occurring words. In accordance with the methodology adopted, each grouping can be understood as the expression of a corresponding set of representational contents - or semantic nucleus (Mossi and Salvatore, 2011). Interpreting the clusters means identifying the thematic core shared by different representational contents conveyed by each group. We consider each semantic nucleus the expression of a specific positioning (Harrè & Gillet, 1994) within the common symbolic space defined by the Symbolic Dimensions, and therefore of a specific way of representing (of having an opinion, of connoting) the various objects of the experience on which the interviewees were invited to express themselves. From this point of view, analyzing the relationship between semantic nuclei and Symbolic Dimensions allows us to understand the socio-symbolic genesis of the representational contents expressed (Mossi and Salvatore, 2012). The association between semantic nuclei and Symbolic Dimensions can be expressed in terms of a quantitative parameter that describes the level of inertia that a given discursive nucleus and a given symbolic dimension have in common: the higher the value of the parameter, the greater the significance of the Association. All analyzes were carried out with the support of a specific textual analysis software: T-LAB.
Here are three orders of results:
- the analysis of the symbolic field configuring the overall discursive dynamic in terms of the two main Symbolic Dimensions that characterize it;
- the analysis of semantic nuclei and their positioning within the symbolic field;
- the interpretation of the illustrative variables in light of the symbolic dimensions;

2.3 Focus Group

The Focus Group is a qualitative data collection technique based on the information that emerges from a group discussion on a topic to be investigated. "Focus" stands for "focused discussion", that is, limited to a limited number of topics that are analyzed in depth (Stewart & Shamdasani, 1990) while "group" identifies the source of information: it is not the individual but precisely , a group of individuals in interaction (Corrao, 2000). The Focus Group therefore allows us to pay attention to meanings, processes and rules that emerge within the group, during the discussion on a specific topic.
The organization of a focus group is divided into 5 phases: Planning, Selection and Recruitment, Group discussion, Data analysis, Return.
In addition to the participants, two are the fundamental figures that make up the Focus Group: the Conductor and the Observer. The conductor clarifies the objectives of the meeting, explains the methods of participation, moderates the debate, facilitates interaction between the participants, makes sure that all participants, and not just some, express their point of view. The Observer, on the other hand, takes note of the non-verbal communication, actively participates in the data analysis and report preparation phase, welcomes the participants to whom he presents himself by describing his function, sits outside the group.
In order to activate and moderate the involvement of the participants, the Conductor has different types of questions at his disposal:
- The Opening Questions allow you to identify the elements in common between the participants (e.g. you are asked to introduce yourself, explain the reason for your presence, say something about yourself in relation to the topic of the meeting)
- The Introduction Questions allow you to introduce the subject of discussion and allow participants to reflect on personal experiences or express their point of view
- Transition Questions bring participants closer to the focus
- The Key Questions introduce the focal and most relevant aspects that are intended to be explored and deepened
- The final questions stimulate the participants to reflect on what has emerged and to identify the aspects discussed (e.g. we ask you to define the most important aspect that emerged during the discussion)
- The closing questions aim to stimulate participants to express their mood and personal opinion regarding the topic and experience.
The Conductor introduces himself, explains the purpose of the meeting, announces the possible

presence for audio / video recording, illustrates the "rules" of participation and invites participants to introduce themselves. Subsequently, the conductor asks some introductory questions / stimuli urging the participants to discuss the topic under discussion in a general way. In our specific case ten different stimuli have been created, created through the recombination of previously determined sentences:

Over the past few months, the public debate on the issue of vaccinations has become increasingly heated.

For some, (3) it is the task of the institutions to take care of their citizens and prepare the conditions for their well-being.

The mandatory nature of vaccines is established precisely in this sense. Getting vaccinated is a duty that everyone is required to maintain safety and public health. It is a moral as well as a legal duty (1).

The debate on vaccines is causing confidence in institutions to falter. Instead, the relationship with close people is strengthened, with whom direct contact can be established (2). It is to those who know each other that one should seek advice (2).

It is the well-being of loved ones and one's own that must be defended. Even violating the law can be justified if it serves to safeguard one's family unit (4).

Institutions, pharmaceutical industries, lobbies of the powerful. What can the citizen do in the face of their overwhelming power? There is nothing we can do. Vaccines today, another thing tomorrow. All that remains is to live the day and rely on fate (5).

The underlined phrases are those that are recombined in the creation of the different stimuli. The numbers between parentheses refer to U.S. of 2.1.
The different stimuli were then made available randomly to the different participants before the start of the discussion. In a third phase, substantial in-depth questions are asked to collect information / data in relation to the purpose of the meeting. In a fourth phase, the conductor makes the return: summarizes the main contents of the discussion, offering participants the opportunity to clarify their point of view. Finally, participants are asked to make a conclusive consideration regarding the discussion.
The interventions of all participants were audio recorded and digitized in Excel folders in the form of a matrix to allow the analysis of the text with the T-Lab software (par 2.2).

2.4 Sampling
For the focus groups, 59 participants (33 women and 26 men) were selected through a sampling of convenience divided into 8 groups. At the end of the focus, the Voc questionnaire was administered. Illustrative variables used: Membership Focus (A1, A2, B1, B2, C1, C2, D1, D2), Participant Gender (SEX_D, SEX_U), Participant Age (AGE_GIO, AGE_ADU, AGE_ANZ), Participant Education (ED_BAS, ED_MED, ED_ALT), Participating Symbolic Universe (US_OU, US_CS, US_IB, US_NB, US_OW)

3.0 Results
3.1 T-Lab Analysis
Through the analysis of the corpus formed by the interventions of all the participants within the focus, we have identified three clusters. For each cluster, 20 characteristic words and a selection of elementary contexts in which these words are found will be reported below. A description of the results will be provided after each cluster.
The segments analyzed by T-Lab (Elementary contexts) are distributed as follows within the clusters:

CLUSTER 1: n=272 50.56%
CLUSTER 2: n=115 21.38%
CLUSTER 3: n=151 28.07%

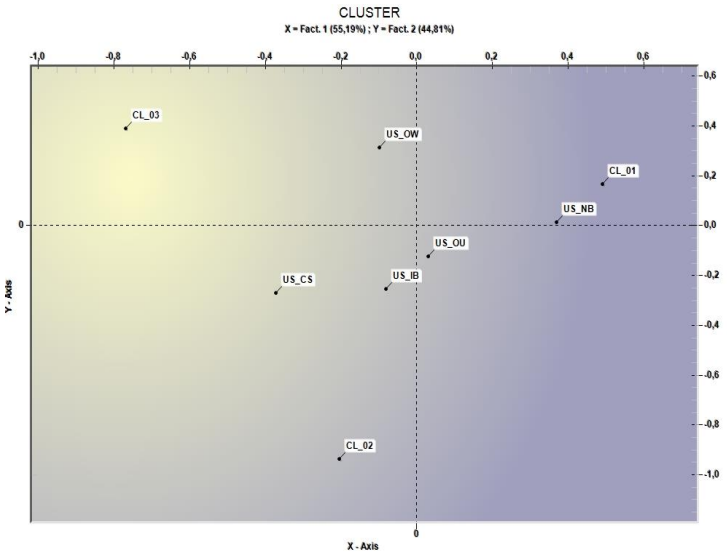
Cluster 1 Interpretation:
Vaccination is seen as something that belongs to the family that is responsible for the decision, decision-making autonomy, the power to decide (Lemmi: we, children, family, take, children, decide, daughter, ours). The rule here has

to do with decision-making power, who is responsible for making the decision to vaccinate or not vaccinate, the family's decision with respect to a health act (Lemmi: mother, take, situation, decide).
Cluster 2 Interpretation:
The idea of the sanction occurs, (paying the fine otherwise they take away your parental authority), the regulatory constraint, therefore vaccination as a norm, the constraint (as opposed to cluster 1), something that society says to do (Lemmi: remove , pay, problem, fine).

Cluster 3 Interpretation:
The scientific / health aspect is predominant in the cluster (Lemmi: disease, flu, virus, vaccine, dying, studies, source).

3.2 Factor analysis
As previously said, the factor analysis allows us to identify the symbolic dimensions that form the semantic field and the positions of the semantic nuclei within it.
Description first dimension / first factor: From the comparative analysis of the two lists of terms and variables we can identify and name the two polarities that form the semantic dimension along which the semantic nuclei are positioned: in the negative pole of the first factor we find speaking, opinion, disease, dying, flu, viruses , history, vaccines, statistics, studies, information, scientific, while in the positive polarity we find thinking, vaccinating, we, school, children, deciding, our, case, child, situation, boy. Proceeding with the abductive construction of a scenario capable of keeping together the relationships between the internal elements at the same polarity and between the two polarities we can define the semantic dimension as a continuum that identifies vaccination as a local / systemic "fact". In the negative pole we have a vision of vaccination as systemic, while in the positive pole vaccination has a local declination, which strictly concerns the sphere of action of the individual.

Description of second dimension / second factor: We use again a process of abductive construction of a scenario that can hold together the relationships between the lemmas within the same polarity and between the polarities: in this case the sense dimension regards the vision of the vaccination which has the characteristics of negotiability / institutional obligation. In the negative pole we find terms such as paying, effect, making a mistake, cause, problem, removing, institution, which we could refer to a scenario in which vaccination is seen as an obligation given by the institution to which it is not possible to escape, while in the positive pole we find terms like thinking, reading, speaking, vaccine, we, people, people, disease, flu, sick who can outline the vision of the vaccine as something that can be negotiated, "I do it because I need it", it's as if vaccination here had to do with the disease. Note that the lemmas present in the positive polarity of factor 2 are similar to those present in cluster 2 and it could not be otherwise, given the proximity between cluster 2 and the position of the US_CS within the semantic field. For the analysis, see the discussion of the results.



The graph shows the distribution that symbolic universes assume within the semiotic space. As can be seen, on the first factor there is an opposition between the (US_NB) and the Caring Society (US_CS) - the first associated with local polarity, the second with systemic polarity. Other's World (US_OW) and Interpersonal Bond (US_IB) take antithetical positions on the second factorial axis - the first on the polarity of negotiability, the second on the polarity of the institutional obligation. The symbolic universe Ordered Universe (US_OU), on the other hand, contrary to what might have been expected, does not occupy a significant position

within the semiotic space. The symbolic universes can be better understood by recalling their location on the factorial axes. The niche of belonging (US_NB) and caring society (US_CS), is consistent with the logic that organizes these symbolic universes: in the first case, since the investment in the primary network responds to the need to survive in an anomalous context, we are inevitably led to put corporal inviolability before the common good; in the second, the reliability attributed to the institutions would induce compliance with public health measures. On the other hand, the opposition between the other's world (US_OW) and interpersonal bond (US_IB) on the second factor is also consistent with the logic with which these symbolic universes are associated: in the first case, the deep mistrust in the world, the sense of powerlessness and anomia and above all the idea that people do not count on each other and pursue selfish objectives, implies a representation of vaccination not in terms of an institutional prescription, but of a practice dictated by an individual choice; in the second, the centrality of relationships and above all the importance attributed to sharing, reciprocity and conformism, is reflected in the adherence to an institutional act, which as such represents a value in itself, which motivates the investment.
Finally, one last observation must be made regarding the ordered universe (US_OU). The immanent order which is presumed to be the basis of this symbolic universe, should be reflected in a systemic and institutional attitude towards vaccination; the fact that the ordered universe does not assume a specific positioning within the factorial space, therefore represents a fact that does not confirm our expectations.

3.3 Conclusions

The results obtained following the research proved to be in line with theoretical expectations: the positions of the US and clusters in the semantic field defined by the dimensions identified through the interpretation of the factors obtained from the textual analysis of the transcripts of the interventions within the focus groups proved compatible. We have seen how the use of ACASM and VOC motivated by the cultural background reported in CAP 1 leads to results that are psychologically relevant and usable by policy-makers for the implementation of targeted intervention strategies. Once the prerequisites of meaning that allow to experience a social phenomenon as such have been identified, it is essential to act through the subjectivity (and not despite the subjectivity) of the individuals who make up the population subject to the intervention to enhance their chances of success. In other words, the identification of the semantic field defined by the sense dimensions of the individuals who create it is a useful condition for identifying how, through culture, the actors configure a certain phenomenon.

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