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An Ontological Framework for the Formal Representation and Management of Human Stress Knowledge

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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Ehsan Nasiri Khoozani

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Table of Acronyms

AACL	Affect Adjective Checklist
ACTH	Adrenocorticotropic Hormone
AI	Artificial Intelligence
ASRA	Automated Systematic Review Agent
CGQ	Common Grief Response Questionnaire
DAML	DARPA Agent Markup Language
DEX-CRH Test	Dexamethasone-Suppressed Corticotropin-Releasing Hormone Test
DILIGENT	Distribute, Loosely controlled, and evolvinG Engineering of oNTologies
DL	Description Logics
DO	Disease Ontology
DO	Domain Ontology
DOGMA	Developing Ontology-Grounded Methods and Applications
DOM	Degree of Membership
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTS	Distributed Terminology System
EBEO	Evidence-Based Evolving Ontology
ESM	Experience Sampling Method
FIS	Fuzzy Inference System
GAD	Generalized Anxiety Disorder
GAS	General Adaptation Syndrome
GCI	General Concept Inclusions
GH	Growth Hormone
GO	Gene Ontology
GSR	Galvanic Skin Response
HC	Hypercortisolemia
HK Ontology	Haghighi-Koeda Mood Disorder Ontology
HPA	Hypothalamic Pituitary Adrenocortical
HSO	Human Stress Ontology
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
IES-R	Impact of Events Scale Revised
LOP	Level of Proof
MAACL	Multiple Affect Adjective Checklist
MBHI	Millon Behavioral Health Inventory
MCMIII	Millon Clinical Multiaxial Inventory II

MeSH	Medical Subject Headings
MGD	Mouse Genome Database
MHO	Mental Health Ontology
MMPI	Minnesota Multiphasic Personality Inventory
NOS	Not Otherwise Specified
OCD	Obsessive Compulsive Disorder
OIL	Ontology Interchange Language
OMIM	Online Mendelian Inheritance in Man
OWL	Web Ontology Language
PDL	Probabilistic Description Logics
PENN	Penn Inventory for Posttraumatic Stress Disorder
POMS	Profile of Mood States
PP	PTSD Patients
PSS	Perceived Stress Scale
PTSD	Post-Traumatic Stress Disorder
RDF	Resource Description Framework
RDFS	Resource Description Framework Schema
SASRQ	Stanford Acute Stress Reaction Questionnaire
SGD	Saccharomyces Genome Database
SLES	Stressful Life Experiencing Screening
SRO	Systematic Review Ontology
SRRS	Social Readjustment Rating Scale
SSS	Subjective Stress Scale
STAI	State Trait Anxiety Inventory
TAS	Taylor Manifest Anxiety Scale
TOVE	TOronto Virtual Enterprise
TRR	Type of Research Results
TSST	Trier Social Stress Test
UMLS	Unified Medical Language System
UNA	Unique Name Assumption
URI	Uniform Resource Identifier
WAS	World Assumption Scale
XML	Extensible Markup Language

Summary of the Thesis

There is a great deal of information on the topic of human stress which is embedded within numerous papers across various databases. However, this information is stored, retrieved, and used often discretely and dispersedly. As a result, discovery and identification of the links and interrelatedness between different aspects of knowledge on stress is difficult. This restricts the effective search and retrieval of desired information. There is a need to organize this knowledge under a unifying framework, linking and analysing it in mutual combinations so that we can obtain an inclusive view of the related phenomena and new knowledge can emerge. Furthermore, there is a need to establish evidence-based and evolving relationships between the ontology concepts.

Previous efforts to classify and organize stress-related phenomena have not been sufficiently inclusive and none of them has considered the use of ontology as an effective facilitating tool for the abovementioned issues.

There have also been some research works on the evolution and refinement of ontology concepts and relationships. However, these fail to provide any proposals for an automatic and systematic methodology with the capacity to establish evidence-based/evolving ontology relationships.

In response to these needs, we have developed the *Human Stress Ontology* (*HSO*), a formal framework which specifies, organizes, and represents the domain knowledge of human stress. This machine-readable knowledge model is likely to help researchers and clinicians find theoretical relationships between different concepts, resulting in a better understanding of the human stress domain and its related areas. The HSO is formalized using OWL language and Protégé tool.

With respect to the evolution and evidentiality of ontology relationships in the HSO and other scientific ontologies, we have proposed the *Evidence-Based Evolving Ontology* (*EBEO*), a methodology for the refinement and evolution of ontology relationships based on the evidence gleaned from scientific literature. The EBEO is based on the implementation of a *Fuzzy Inference System* (FIS).

Our evaluation results showed that almost all stress-related concepts of the sample articles can be placed under one or more category of the HSO. Nevertheless, there were a number of limitations in this work which need to be addressed in future undertakings.

The developed ontology has the potential to be used for different data integration and interoperation purposes in the domain of human stress. It can also be regarded as a foundation for the future development of semantic search engines in the stress domain.

Chapter 1 – Introduction

1.1 Introduction

This chapter provides an overview of the research and advances made in various dimensions of the *human stress* and *ontology* domains. We initially offer a summary of the historical roots of the stress concept and its evolution in the scientific literature over time, as well as a description of its various dimensions in the domains of physiology and psychology. Subsequently, we present a brief introduction to *knowledge engineering* and *knowledge-based systems* as a framework within which ontology and ontology-based techniques have been implemented for various knowledge acquisition and management purposes. Then, we present an overview of the philosophical trends in knowledge engineering and ontology concept followed by the definition of ontology, ontology relationships, and a description of several ontology applications in various areas of computer science and knowledge engineering. This chapter concludes with an explanation of the motivation for this thesis and sketches its goals, scope, and significance followed by a section about the structure of the thesis and conclusion.

1.2 Stress

The concept of *stress* in physiology and psychology domains can be defined as the organism's adaptive physiological, cognitive and behavioural responses to challenging and harmful conditions. These responses may involve various processes, from gene expression to different social interaction (Monroe, 2008).

1.2.1 Stress History

The term 'stress', originating from the Latin words *strictus* (tight) and *stringere* (to tighten, to pull tight) (Lazarus, 2006; Selye, 1956), was adopted first in the 14th century to describe hardship, strain, or suffering (Lumsden, 1981). Later, Robert Hooke, a physicist and biologist of the late 17th century explained stress from the engineering perspective. He adopted three concepts of load, stress, and strain to describe the resistance requirements of structures such as bridges against the striking effects of natural forces such as earthquakes or winds. In his analysis, *load* implies external forces such as weight; *stress* refers to the section of the bridge's structure over which the load exerts pressure; and the consequent deformation of the structure, which is created by the interaction of load and stress, is called *strain* (Lazarus, 2006).

This account of stress in engineering terms inspired the models of stress in the 20th century where the external forces (stress stimuli) on a social, psychological, or physiological system were considered to be analogous to the concept of *load.* Respectively, stress response was analogous to strain. Later, the term *stressor* or stress stimulus was adopted to describe external forces, and *stress response* (*reaction*) was used to explain the consequences of such stimuli (Lazarus, 2006; Selye, 1950a).

However, historically, there has been inconsistency across various fields of study regarding the application and meaning of such terms. For example, physiologists used the term *strain* to refer to physiological alterations and deformations caused by stressors. In contrast, sociologists used the same term to describe pressures in the social system, and employed the term *stress* when referring to people's reactions to those pressures (Lazarus, 2006).

1.2.2 Stress and Adaptation

In the realm of physiology, the concept of stress is tightly linked to the concepts of *adaptation* and *homeostasis*. Stress has even been defined by some theorists as the organism's threatened homeostasis (Charmandari, Tsigos, & Chrousos, 2005). Claude Bernard, one of the earliest contributors to the study of stress, discovered the role of insulin deficits in some physiological dysfunctions such as diabetes or mental confusion. This discovery led physiologists and biologists to consider the concept of *homeostasis* as a mechanism through which the organism maintains its internal balance in order to survive. For example, the body needs to maintain correct levels of sugar, oxygen, water, etc to stay alive (Lazarus, 2006).

The ideas of Claude Bernard indirectly affected current approaches to *adaptive processes* and *survival*. In this respect, adaptive actions such as shelter seeking and flight were viewed as mechanisms contributing to individuals' survival. However, it was observed that such actions and struggles for survival may also end up disrupting the organism's state of homeostasis (Cannon, 1939). Canon noticed that in order to respond to a threatening situation with a *fight or flight response*, the organism must mobilize its bodily resources. In turn, the intense and long-lasting effects of anger or fear, as a result of those energy mobilizations, can be stressful and damaging to the body. Later, in pursuit of Bernard's and Canon's discoveries, Hans Selye (1956) formulated his prominent theory of stress in physiology.

In an attempt to abstract common features of all diseases, regardless of each one's typical characteristics, Hans Selye initially used the phrase "*syndrome of just being sick*". He observed that all organisms would show some common reactions to imposed stimuli such as excessive high or low temperature, noise, pain, or any perceived challenge or strain regardless of each stimulus' individual characteristics. Hence, such reactions, despite their different specific features, share some common non-specific characteristics such as appetite loss, high blood pressure or decrease in muscular strength which were abstracted by Selye as *stress* (Cooper, 2004; Selye, 1950b). This concept could explain the physiological processes through which the body mobilizes its resources in response to threatening and harmful situations. Later, Selye postulated the theory of *General Adaptation Syndrome* (GAS) to describe those neuro-chemical and physiological alterations undergone by the body to defend itself against noxious stimuli (Selye, 1956).

1.2.3 Various Dimensions of Stress

Historically, there have been many attempts by sociologists, psychologists, and physiologists to describe individuals' struggles for adaptation using different terms such as *conflict*, *frustration*, *trauma*, *anxiety*, *depression*, *alienation*, or *emotional distress*. After the term *stress* became prominent in the literature, researchers who had been studying different concepts with some kind of similarity or connectedness to the concept of stress replaced their previous terms with the term stress, while maintaining their own lines of investigation. Stress was adopted as a term which could integrate various concepts about different causes and emotional outcomes of individuals' struggle to manage their daily life tensions (Lazarus, 2006).

Various physiological and psychological viewpoints on the concept of stress have highlighted a variety of dimensions or mechanisms which are involved in this phenomenon. These perspectives have identified a diversity of physiological and psychological stressors and have attempted to explain how those stressors engage the organism's physiological and psychological functions with their consequent adaptive or maladaptive outcomes. The multiplicity of these theories gradually persuaded some researchers to recognize the existence of multiple dimensions of the stress phenomenon (Lazarus, 2006).

Initially, researchers tended to consider stress as a uni-dimensional concept or a continuum (similar to activation and arousal) which can range from low to high (Duffy, 1962). However, later researchers outlined different types of stress such as *eustress* and *distress* (Selye, 1974). Eustress was defined as the constructive type of stress which could be demonstrated by those types of emotion which are related to positive endeavours or empathy for others. Eustress is supposed to be a promoter or protector of well-being and health. In contrast, distress is manifested as negative emotions such as anger or aggression and purports to harm the individual's health. Nevertheless, there is still ambiguity and controversy over this hypothesis of stress since empirical research has not yet been able to support or refute this hypothesis (Lazarus, 2006).

Another dimension of stress relates to the *specificity* versus *non-specificity* of stress response. Selye first defined stress as the organism's *non-specific* response to any demand (Selye, 1974). However, later studies showed that there exist specific responses to different types of physiological or psychological stressors. For example, according to the theory of *primitive specificity*, specific *neuro-chemical signatures* can be produced by the effect of each stressor type which, in turn, engage different central or peripheral mechanisms in distinct qualitative or quantitative ways (Pacak & McCarty, 2007). Other studies have outlined the role of psychological factors in the elicitation of stress-induced neuro-chemical alterations (Mason et al., 1976; Pacák & Palkovits, 2001).

In another line of study, Lazarus (1966) distinguishes three types of psychological stress (harm/loss, threat, and challenge) which are based on different appraisals. *Harm/loss* implies a harm or loss which has already occurred, whereas *threat* indicates harm or loss which is perceived as probably imminent. Respectively, *challenge* refers to the feeling that the individual is able to conquer hardships that are located on his/her way and reach the goal by vigour, perseverance, and self-confidence. People tend to cope with each type of these stresses in a different way. As a result, the psycho-physiological and functional consequences of each stress type are different (Lazarus, 2006).

Furthermore, the stress phenomenon has been demonstrated to be even more complicated when its dimensional, mediated, relative, and contextual effects on different individuals are considered. Researchers (e.g. Harris, 1991) over the decades have shown that stress can engage a broad array of psychological and physiological mechanisms and have different temporary or lasting effects on cognitive, emotional or physiological functions which are being mediated by various cognitive (Lazarus & Folkman, 1984), physiological (Lupien et al., 1994) or situational (Kopp, Skrabski, & Szedmák, 1998) factors.

1.3 Knowledge Engineering and Knowledge-based Systems

Before introducing the concept of ontology and its applications, it is worth presenting a brief description of the knowledge engineering field since ontology and ontology-based techniques were initiated in this field.

Knowledge engineering is a branch of computer science which incorporates methods and techniques for the integration of knowledge into computer systems. It aims to establish, maintain and develop knowledge-based (expert) systems[1] in order to reduce the need for having high level expertise for solving complicated problems (Feigenbaum & McCorduck, 1983). Knowledge engineering has also broad associations with and applications in domains such as *artificial intelligence*, *data mining*, *expert systems*, *mathematical logic*, and *cognitive sciences* (Negnevitsky, 2005).

1.3.1 Philosophical Trends in Knowledge Engineering

Knowledge acquisition and knowledge representation strategies and techniques have their roots in philosophy and epistemology. Philosophers in their attempts to answer questions such as "*How do we know what is true and real about the world*?" or "*In what way is knowledge really a representation of reality*?" have developed different epistemological standpoints on the basis of which various methodological perspectives have been established. The solutions and proposals offered by such approaches regarding the reliability criteria of the acquired knowledge have primarily been challenged by another basic question: "*What is the nature of knowledge* (Compton & Jansen, 1990)*?*"

By and large, answers to these questions have formed two basic epistemological theories: a) *reductionist approach*, and b) *non-reductionist approach* (Compton & Jansen, 1990).

a) According to a reductionist theory, knowledge is made of symbols of reality and their relationships. This theory, which is well represented in the *Physical Symbol Hypothesis* (Newell & Simon, 1976), holds that in the process of knowledge acquisition, the fundamental atoms of knowledge and their logical relations must be discovered.

b) Unlike the reductionist view of knowledge representation, which was a common perspective among early *Artificial Intelligence* (AI) researchers, a non-reductionist approach considers the conceptualization of theories, regardless of the correspondence of such models

[1] Knowledge based (expert) systems are part of artificial intelligence tools which are used for the acquisition, representation, and documentation of knowledge as well as various intelligent decision support, machine learning, and reasoning purposes (Akerkar & Sajja, 2009).

to the real world. In this case, although the proposed formulations of a certain theory might not be true or in accordance with the reality, the development of acceptable and consistent conceptualization systems, through abstract representations of a domain entities and their relationships, can have useful applications. In this regard, such conceptualization systems, with their special language and terminology, may contain facts that hold true within a specific domain for a community of users, regardless of their applicability and truthfulness in other knowledge domains (Compton & Jansen, 1990; Smith, 2003). This view of knowledge and its representation triggered the creation of knowledge-based systems and knowledge engineering ontologies (Sowa, 1995).

Historically, the development of knowledge-based systems began with the *transfer perspective* according to which the existing knowledge possessed by the domain experts can be simply collected (e.g. through interview) and transferred into a knowledge-based system. The acquired knowledge, then, could be represented in the form of rules such as the production rules implemented in industrial environments. This view, which was the predominant view in the 1980s, was later found to be inadequate in representing different types of knowledge, since it had resulted in a number of problems with respect to the maintenance of knowledge bases. Numerous experiences showed that the knowledge required to equip an expert system with sufficient problem-solving capacities cannot be limited to the transferable *explicit* knowledge of a domain expert, but, the *implicit* or tacit knowledge of domain specialists also plays an important role in efficient problem-solving strategies (Studer, Benjamins, & Fensel, 1998).

Such experiences led knowledge engineers to develop a *modelling process perspective* toward the building course of knowledge-based systems. According to this approach, knowledge-based systems can be considered as computer models that aim to simulate different problem-solving capabilities of domain experts. In this way, the expert's tacit and implicit knowledge can be acquired, structured, and modelled during the course of knowledge acquisition. However, it has been acknowledged that the resultant models can only be an approximate similitude of the reality. Furthermore, it was suggested that modelling must follow a cyclical process, responding to new observations via refinement, modification, and incremental construction of the established models. It was also recognized that every modelling outcome requires evaluation and revision as it is likely to be influenced by the subjective, and even faulty, interpretations of the domain experts (Studer, Benjamins, & Fensel, 1998).

1.3.2 Development of Various Problem-Solving Methods

Adoption of the modelling process perspective resulted in the development of different problem-solving behaviours and *reasoning* methods for various knowledge-based systems. Overall, each problem-solving method defines a certain type of inference action which can be utilized for solving an intended task. For instance, the *heuristic classification* problem-solving method employs three central inference actions of *abstract*, *heuristic mach*, and *refine*, to find a solution for a given problem. Furthermore, the notion of *knowledge roles* was proposed to specify the kind of role a domain knowledge can play in each inference action. Knowledge roles such as *observables*, *abstracts*, or *solutions* can be identified by examining various domain-dependent and generic terminologies of the knowledge domains (Studer et al., 1998).

This variety of problem-solving methods and techniques has resulted in the development of different models of expert systems such as CommnKADS (Schreiber, Welinga, Akkermans, Van De Velde, & de Hoog, 1994), MIKE (Angele, Fensel, Landes, & Studer, 1998) and PROTÉGÉ-II (Eriksson, Shahar, Tu, Puerta, & Musen, 1995).

PROTÉGÉ-II is one of the earliest knowledge-based system models which employed ontologies in order to support the reuse of domain conceptualizations and problem-solving methods as well as the development of ontology-based knowledge acquisition tools. To solve a given problem or perform an intended task, PROTÉGÉ-II's problem-solving methods decompose it into smaller subtasks so that it can become solvable by the mechanisms or methods which are available in the knowledge-based system. To specify the inputs, outputs, concepts, and relationships utilized by problem-solving methods, a *method ontology* is built. This ontology aims to capture generic terminology and concepts which are related to the knowledge roles (Studer et al., 1998).

The *domain ontology* is another type of ontology used by the PROTÉGÉ-II to define a domain's shared conceptualization. Moreover, the use of an *application ontology* is introduced to incorporate *specific* concepts and relationships relevant to the problem-solving methods in order to link the domain ontology to the method ontology. Overall, through the specification of meta-level conceptualization of knowledge bases, ontologies were proposed to support the reuse of knowledge bases and offer solutions for the interaction problems that might exist between the domain knowledge and problem-solving methods of the expert systems (Studer et al., 1998).

1.4. Ontology

The term *ontology* in computer sciences was originally adopted from philosophy. Ontology in philosophical terms (metaphysical ontology) can be defined as the science of what exists, dealing with all categories and structures of objects, processes, events and their associations in every field of reality (Smith, 2003).

The scheme of a metaphysical ontology inspired researchers and experts of information sciences and knowledge engineering to develop shared and consistent representation frameworks, under the name of ontology, for different domains of knowledge. One of the main purposes of having such an ontology in this field was to explicitly represent various concepts and the relationships between them in formal categories and classification systems. However, it has been emphasized that ontological definitions and classification systems in both philosophy and computer sciences are relative and that the possibility of developing a normative ontology sounds somewhat challenging (Sowa, 1995).

1.4.1 Ontology Definition and Characteristics

Overall, ontology in the computer sciences can be defined as a branch of knowledge engineering which aims to present formal and explicit descriptions, definitions, classifications, and organization for the existing concepts and their associations in a knowledge domain. In other words, as Gruber (1993) described, ontology is the formal and explicit specification of a domain conceptualization. In this definition "*formal*" implies mathematical description and machine readability of knowledge representation. "*Explicit*" refers to the explicitness, clarity, and precision of the defined concepts, their relationships and constraints. For example, an explicit definition of the concepts *disease* and *symptom* in the medical domain may hold that they have a *causal* relation with each other with the *constraint* that a disease cannot be the cause of itself. Respectively, "*domain conceptualization*" points to the establishment of an abstract model or view of a phenomenon, i.e. abstracting the concepts and the relationships between them which might exist in a certain domain (Hadzic, Wongthongtham, Chang, & Dillon, 2009; Studer et al., 1998).

Ontology can also be characterized by its *sharable* nature. Ontology, therefore, is considered to be a reference source on the basis of which diverse applications within a knowledge domain can be managed. The content of a shared ontology is basically agreed upon, accepted, and committed to by various applications (Hadzic et al., 2009). However, the shareability and consensuality of an ontology is context-dependent and relies largely on the ontology's purpose of use and community of users. For example, an ontology of medical terminology used within a hospital must be agreed upon mainly by the doctors who deal with that terminology within the context of that hospital (Studer et al., 1998).

It has also been emphasized that ontology models are flexible and modifiable models. Hence, the evolution of knowledge in a domain entails the concurrent evolution of its representation (Helsper & van der Gaag, 2002).

1.4.2 Ontology Structure

Ontology-based conceptual modelling and representation are normally hierarchical models. This is concordant with the natural tendency of the human mind to organize mental models through the formation of hierarchies. Hierarchies also facilitate the task of specialization and generalization (Guizzardi, 2005; Rosch, 1978). Nevertheless, ontologies can also be developed into graph structures or network models in order to meet the more complex requirements or goals (e.g. reasoning) of an expert system (Helsper & van der Gaag, 2002).

1.4.3 Ontology Relationships

Ontology relationships are linkages which are defined between ontology concepts or entities. *Concepts* in every domain of knowledge symbolize the phenomena that experts in that domain deal with; and *relationships* establish meaningful connections between those phenomena.

1.4.3.1 Types of Ontology Relationships

Despite the existence of various types of concepts in different domains, the relationship types across domains bear many commonalities. For example, almost all ontologies make use of the taxonomy (is-a) or meronomy (part-of) relationship types in their conceptualizations.

Overall, the different types of relationships within ontologies can be categorized into two groups: 1. *structural relationships*, and 2. *operational relationships* (Nasiri Khoozani, Hussain, Dillon, & Hadzic, 2010).

Structural relationships refer to those static relationships such as “is-a” or “part-of” which imply the constancy and necessity of structural connections between the objects of a domain. The finite concepts in most of the ontologies are linked together using this type of relationship. The classification and categorization tasks in ontologies are typically based on the structural type of relationships.

Conversely, operational relationships indicate the existence or process of dynamic interactions between entities and the influences that different phenomena have on each other. Such influences can take various forms including causation, alteration, regulation, mediation, etc. In this regard, operational relationships in scientific domains represent *scientific laws* by identifying the existing connections between different entities and describing the discovered influences that those entities have on each other (Nasiri Khoozani et al., 2010).

1.4.3.2 Defining Ontology Relationships

Ontology relationships in different domains are defined mainly via the consensus of domain experts. For example, in business domains, an agreement can be reached between professionals or stakeholders that the relationship "*provide*" connects the two ontology concepts of "*supplier*" and "*material*" in this way: *Supplier provides material*. However, when it comes to scientific fields, a mere consensus-based strategy for the establishment of ontology relationships sounds less viable. Therefore, it has been emphasized that the defining of ontological relationships between concepts in scientific domains (e.g. biomedical ontologies) would be grounded in already established scientific facts (Smith, 2004). For example, an ontological statement such as "*cell cycle checkpoint regulates cell cycle*" in Gene Ontology (GO) (Gene Ontology Consortium, 2006) has not been defined based on mere consensus, but it is grounded in the scientific fact that the cell cycle is constantly and necessarily regulated by the cell cycle checkpoint (Gene Ontology Consortium, 2006). Likewise, we propose that it is desirable that the establishment of ontological relationships in the HSO be based on the scientific evidence which is obtained from scientific literature.

1.4.4 Ontology Applications

1.4.4.1 Ontology for Data Mining and Reasoning Tools

A fundamental characteristic of an ontology, which makes it a useful tool in the knowledge engineering domain, is its machine-readability feature. The concepts and relationships contained in an ontology framework can be accessed, retrieved, understood, analysed, and managed by different automated computer programs and agents. For example, data embedded in a body of knowledge can be accessed and analysed in an intelligent manner by automated programs such as *data mining*[2] tools (Goméz-Pérez, 1998). Data mining techniques are a set of processes which facilitate detection of patterns and knowledge embedded in a large quantity of data for the purpose of better understanding the data, finding hidden patterns in the data, and establishing predictive models based on those data (Fayyad et al., 1996).

Moreover, the machine readable definitions of concepts in ontology facilitate the process of terminological reasoning. Ontology is capable of reasoning about the concept meanings by making comparisons between logical concept structures. An instance of such a reasoning capability is reasoning about the subsumption relations via a process of comparison between logical definitions of each concept in order to define whether a certain concept subsumes another. In this way, if, for example, concept *A* meets the criteria of being a member of concept *B*, then it will be classified under concept *B* in an automatic way. As a result, ontologies can facilitate the tasks of query processing and searching in various applications (Beck & Pinto, 2002).

1.4.4.2 Ontology for Communication and Interoperation

Facilitation of communication and interoperation is another central utility of an ontology framework. The act of every communication process between two or more agents[3] relies primarily on the capability of those agents to understand and make understood each other's language, terms, or expressions. The importance of ontology, therefore, relates to its utility as

[2] Data mining methods aim to *predic*t and *describe* a given set of data. In the prediction process, some identifiable variables or fields in the database are used in order to predict the unidentified values of desired variables. Description aims to discover descriptive patterns in the data which are interpretable by humans. There are a number of data mining methods for the prediction and description tasks. These may include classification (learning to map an item into a relevant predefined class), regression (learning to map an item into a prediction variable), clustering (description of the data through identification of a limited set of categories), summarization (presenting a unified description for a subset of data), dependency modelling (discovering a model for the description of significant dependencies between data), and change and deviation detection (identification of the most significant alterations in the data compared to their previous measured or normative values) (Fayyad, Piatetsky-Shapiro, & Smyth, 1996).

[3] An agent is defined as an autonomous computer system located in a certain environment for the performance of certain objectives (Wooldridge, 2002).

a facilitator of effective understanding and intelligent communication processes. Ontologies are able to define, interpret, translate, and represent the terms and concepts used by various agents, ensuring that *same terms* have *same meanings* for different communicating agents. This can be achieved through the agents' employment of one consensual and common ontological framework for their intended domain of knowledge (Hadzic et al., 2009).

Furthermore, a single community is able to employ different ontologies when aiming to communicate with different agents. On the other hand, the common knowledge of various agents can be retrieved to create a shared ontology (Hadzic et al., 2009).

1.4.4.3 Ontology for Data Integration

A further communication-facilitating utility of ontology is its role in the process of *data integration*. Data integration includes unification of data embedded across various data sources in order to obtain a common view of those data (Lenzerini, 2002). Ontology is useful for eliminating *data heterogeneities* and has applications in areas such as enterprise information integration and medical information management (Cruz & Xiao, 2005). Further details about this application of ontology are presented in Chapter 3.

1.4.4.4 Ontology for Systematic Review

1.4.4.4.1 Systematic Review

It has been emphasized that scientific theories in different fields of science must be based on evidence. For this reason, the methodological strategies of systematic review and meta-analysis were proposed to obtain a correct account of the best existing evidence for a certain theory. Systematic reviews are succinct summaries of the best available evidence for a scientific hypothesis or question. Using the explicit methods of systematic review, researchers are able to identify, analyse, examine, and integrate reliable evidences which are obtained from a multitude of various research reports. Taking this all-encompassing approach, they go beyond individual evidences and try to determine "*the whole truth*"

(Mulrow, Cook, & Davidoff, 1997). In this way, they ensure the creation of more valid scientific statements. Hence, systematic review supports the collaborative and cumulative nature of science, aiming to integrate isolated and disunited segments of related research results in one framework (De Almeida Biolchini, Mian, Natali, Conte, & Travassos, 2007).

There are a few systematic review approaches researchers can use to acquire a comprehensive account of various published research results. The *election mode* or *voting method* is one of the simplest methods of systematic review.

Using a voting method, the researcher can examine each study separately and count up their results in terms of the corroboration or disproof of a research hypothesis.

However, the complexity, context dependency, and variation of conditions across different research works are less likely to be captured by a simple counting method. As a solution to this problem, more advanced statistical methods such as *meta-analysis* were invented to enable researchers to analyse data and different aspects of each study as well as overcome the problem of subjectivity and bias in choosing or disqualifying certain studies (Stanley, 2001) and moderate relative biases which might exist in various primary individual studies (De Almeida Biolchini et al., 2007).

1.4.4.4.2 Application of Ontology for the Facilitation of Systematic Review

There have also been some efforts to use ontology as a facilitating tool in order to streamline the process of systematic review.

The process of systematic review begins with the explicit and precise formulation and definition of the central research question. In this respect, the research question can be regarded as a multidimensional *conceptual structure* which guides other stages of the systematic review process. However, there may exist controversies and disagreements on the meaning and semantics of this conceptual structure. Formulation of a consistent and agreed conceptual structure and achievement of relevant and comparable results entail using a shared controlled vocabulary (De Almeida Biolchini et al., 2007). To this end, De Almeida Biolchini et al. (2007) propose the establishment of a *scientific research ontology* where we can render a shared and formalized specificaton of the concepts involved in the conceptual structure of the systemtic review.

The implementation of such an ontology framework purports to explicitly formulate the core research question and provide different researchers with terminological homogeneity as to the definition of the concepts they use and, thereby, ensure consistency between retrieved information and the consequent results. It can also be considered as a streamlining instrument based on which information extraction tools can identify, extract, and link the scientific terms which are embedded within different scientific texts (De Almeida Biolchini et al., 2007).

This type of ontology should take advantage of both the hierarchical structure and semantic content, incorporating basic categories of concepts which are relevant to various knowledge domains involved in the systematic review process. Such knowledge domains may comprise information elements and structures related to the scientific method or different experimental methods applied in various researches. For example, an ontology for the *experimental method* may include concepts such as *problem*, *hypothesis*, or *variable*, etc. On the other hand, a *primary study ontology* may include conceptual relationships such as "*hypothesis has formulation*". There can also be links between concepts of different ontologies (e.g. between the experimental method ontology and primary study ontology) in order to realize a more applicable and robust ontology for the systematic review (De Almeida Biolchini et al., 2007).

1.5 Motivation for This Thesis

The existence of dispersed and disorganized information about human stress across diverse databases, and the lack of an ontology framework in this field, motivated us to design the initial version of the Human Stress Ontology (HSO). The use of ontologies in different medical and biomedical domains has already proven to be effective and helpful in the process of data organization, management, and search. Therefore, inspired by those attempts, we decided to develop the HSO as a potential solution to a number of data management and retrieval issues in the stress domain. This initiative was particularly in line with recent world-wide attempts to develop and replace the Semantic Web with the current form of Web. Moreover, to the best of our knowledge, this project was considered to be one of the first ontology frameworks being established in the fields of psychology and psychiatry.

We were also motivated by the difficulty and complexity of defining dynamic relationships between the HSO concepts and the need to establish evolving and evidence-based relationships between the concepts in the HSO and other scientific ontologies.

1.6 Research Goals

The goals of this research are:

1. To establish an ontological framework for the concepts and theories within the domain of human stress so that the dispersed and interconnected information in this field can be organized, linked together, and formally represented in a meaningful way. It is envisioned that the proposed ontology will facilitate the process of data integration and provide a foundation for the design of intelligent programs such as semantic search engines and data mining tools for effective search, retrieval, and analysis of stress-related information.

2. To develop an ontology evolution methodology through which the dynamic and operational relationships in the HSO and other scientific ontologies can be modulated and evolved based on the received evidence from scientific databases. Moreover, we aim to consider systematic review as a practical strategy based on which an evidence-based account of ontology statements can be established.

1.7 Research Scope

The scope of this research primarily encompasses:

1. Development of an ontology framework for the conceptualization and formally representation of stress knowledge within the domains of *psychology* and *psychiatry*, and evaluation of this ontology framework.

2. Finding a solution for the establishment of evolving/evidence-based ontology relationships between concepts of stress domain.

1.8 Research Significance

The development of the HSO and EBEO methodology have some significances for both stress and ontology domains.

1.8.1 The Significance of the HSO

- The primary significance of the HSO is that, to the best of our knowledge, it is the first ontology framework designed specifically for the domain of human stress. In this regard, we have created a formal framework with which the current disorganized and dispersed knowledge of stress can be integrated, linked together, and represented in an organized and meaningful way.

- The HSO has the potential to provide an overview of various research subjects and empirical findings such that different subjects, concepts, and empirical results can be placed in their proper categories and viewed in relation to one another. Therefore, through the unified and incorporative structure of the HSO, some formerly unseen relationships among different aspects of theories and concepts are likely to be revealed, motivating researchers to carry out additional studies to address any gaps or other latent issues across entities and theories. For example, an ontology as such can explicitly explain the potential relations a set of data have with multiplicities of other theories and methods which have addressed relevant aspects of the same phenomenon.

- The development of a formal, explicit, and common vocabulary (terminology) framework for the stress domain has the potential to help researchers retrieve desirable information, make consistent statements, draw reliable conclusions, and communicate effectively with one another.

- The HSO has the potential to facilitate the integration of heterogonous information resources within the stress domain and help experts manage the contents of different databases in relation to one another. Employment of the HSO and its related ontologies can potentially enable different information systems to interoperate with each other.

- It can be a basis for the development of ontology-driven software tools for different information retrieval, analysis, and pattern-discovery purposes. For example, the HSO can potentially be applied to the design of Semantic Web engines through which desired information can be retrieved, accessed, managed, and analyzed in an intelligent and meaningful way.

- The HSO can be potentially helpful in clinical situations by enabling clinicians to readily and effectively access desired information.

- The HSO can be considered as a motive for the development of other ontologies in psychology and psychiatry domains.

1.8.2 The Significance of the EBEO Methodology

- The proposed ontology evolution solution (EBEO) has the potential to augment the accuracy and evidentiality of ontology relationships. In this regard, the establishment of evidence-based and evolving domain ontologies can provide investigators with information about the latest research outcomes related to the degree of corroboration or refutation of a scientific theory in the form of explicit ontological facts.

- The continuous process of retrieval, examination, and representation of research conclusions through EBEO can potentially assist researchers to write more comprehensive and accurate state-of-the-art reports.

- The implementation of the Automated Systematic Review Agent (ASRA) and Fuzzy Inference System (FIS) in this methodology may motivate researchers to develop special ontology tools for the incorporation of evolving/evidence-based ontology relationships.

1.9 Thesis Structure

This thesis is structured as follows:

Chapter 1- Introduction. In the first chapter we initially introduced the concept of stress and drew on the field of knowledge engineering, ontology, ontology relationships, and a number of ontology applications. Subsequently, we explained our motivation for accomplishing this project and outlined the research aims, scope, and significance.

Chapter 2- Literature Review. Chapter 2 provides an overview of some of the previous categorization systems for stress-related phenomena in the fields of psychology and psychiatry and elaborates on a few established ontologies in biomedical, medical, and mental health sciences. It also describes some of the most widely used ontology-building methodologies, ontology languages and ontology tools. Subsequently, previous attempts to refine and evolve ontology relationships are summarized. The chapter ends with a critical review of previous research works and highlights the role of our project in filling the existing gaps and missing points.

Chapter 3- Research Issues. Chapter 3 initially defines the significant concepts which are frequently used in this thesis. Then, it describes some of the research problems and issues which have been addressed in our work. It also describes how the choice of ontology and EBEO methodology can offer solutions for those problems and issues.

Chapter 4- Overview of the Solution. This chapter offers a brief overview of the stages we undertake to solve the research problems and issues. Subsequently, the objectives of our thesis are listed in this chapter.

Chapter 5- Research Method. This chapter describes the methodology which we have employed for the development of the HSO and elaborates on its different stages. It also presents a brief description of the proposed methodology for the refinement of ontology relationships.

Chapter 6- Conceptualization and Classification of Human Stress Knowledge. This chapter describes the conceptualization, classification and structure of the HSO. It offers a broad review of stress-related literature and explains different sub-ontologies and categories of the HSO.

Chapter 7- Formalization of the Conceptualization. This chapter draws on the formalization of the HSO. It elaborates on OWL, the ontology language which has been implemented for the formalization of the HSO. The HSO visualization by means of ontology tool, Protégé 4, is also explained in this chapter. We present a number of visualization figures which helps the reader understand different functions of OWL ontologies and Protégé tool.

Chapter 8- Development of a Methodology for the Evolution of Ontology Relationships. Chapter 8 explains the proposed methodology for the evolution and refinement of ontology relationships between HSO concepts.

Chapter 9- Evaluation of the HSO and Illustration of the EBEO Methodology. The process and results of our evaluation of the HSO are presented in Chapter 9. This chapter also illustrates the envisioned implementation of the EBEO methodology.

Chapter 10- Recapitulation, Limitations and Future Work. The last chapter recapitulates and concludes this thesis. It also points to the limitations we have faced and offers some suggestions for the future works.

1.10 Conclusion

This chapter defined and explained the stress phenomenon and its various dimensions as this concept evolved throughout its history in the physiology and psychology domains. It also introduced and described the role of ontologies in knowledge engineering and knowledge-based systems for various purposes of data management, data mining, reasoning, data interoperation, data integration, and systematic review.

It was emphasised that the complexity and multidimensionality of the stress phenomenon resulted in researchers carrying out numerous research works in the stress field. The results of such research works have been stored in a dispersed and disorganized manner. We explained how the existence of such dispersal and disorganization within stress-related information across various databases and the lack of an ontology framework in this field motivated us to consider the design of the HSO as a potential solution.

Furthermore, we described the role and characteristics of ontology relationships and emphasized the importance of defining evolving and evidence-based relationships in scientific fields.

Our research aims to design an ontological framework for the organization and connection of stress-related information, and to find a solution for the establishment of evolving/evidence-based ontology relationships.

Finally, we described the significance of thesis and the contribution that the HSO and EBEO will potentially make to stress and ontology domains. In the next chapter, we present an overview of the previous research works on the organization of stress knowledge and describe some of the examples of the established ontologies in medical and mental health domains.

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Chapter 2 –Literature Review

2.1 Introduction

This chapter introduces some of the previous endeavours undertaken for the categorization of stress-related concepts in psychology and psychiatry. It also presents a review of some of the established ontologies in biomedical, medical, and mental health sciences and highlights their important characteristics. Subsequently, some of the existing ontology-building methodologies, ontology languages, and ontology-building tools are reviewed. Then, a brief description of previous efforts for the refinement and evolution of ontology relationships is presented. In the end, we present a critical review of previous attempts and highlight the shortcomings to be addressed by this thesis.

2.2 Previous Attempts to Classify Stress-related Concepts

2.2.1 Selye's Symbolic Short-hand System for Medicine and Physiology

The earliest effort to classify information and research results related to stress phenomena was made by Selye (Everly & Lating, 2002). Having tried to classify a huge variety of information under their related categories, Selye designed a "*Symbolic Short-hand System for Medicine and Physiology*" (Selye & Miklos, 1958) in order to facilitate the process of finding associations between various concepts and categories. Through the implementation of a number of signs and arrows, this system enabled the researcher to manually access the desired information (Everly & Lating, 2002).

2.2.2 Classification of Coping Strategies

Since Selye's early attempt, a number of other taxonomies for the classification of some stress-related concepts such as coping strategies (Ryan-Wenger, 1992) have been introduced by different researchers. For example, in his categorization system of *children coping strategies*, Ryan-Wenger (1992) defined fifteen basic categories of coping strategies including:

- Aggressive Activities
- Behavioural Avoidance
- Behavioural Distraction
- Cognitive Avoidance
- Cognitive Distraction
- Cognitive Problem-Solving
- Cognitive Restructuring
- Emotional Expression
- Endurance
- Information Seeking
- Isolating Activities
- Self-controlling Activities
- Social Support
- Spiritual Support
- Stressor Modification

2.2.3 Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)

The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association, 2000) is a prominent categorization system for psychiatric diagnoses. Published by the American Psychiatric Association, this handbook incorporates all identified mental health disorders, descriptions of their known causes, and related statistics as to gender and age-related factors, prognosis, and recommended treatment strategies.

The DSM-IV can be regarded as a basic classification system in the field of stress-related disorders which incorporates a prominent categorization of *Anxiety Disorders*. The DSM-IV classifies anxiety disorders on the basis of their causes, symptoms, or both (Everly & Lating, 2002). The category of anxiety disorders includes the sub-categories of:

- Generalized anxiety disorder
- Panic disorder
  - Panic disorder with agoraphobia
  - Panic disorder without agoraphobia
- Agoraphobia without history of panic disorder
- Specific phobia
- Social phobia
- Obsessive-compulsive disorder
- Post-traumatic stress disorder
- Acute stress disorder
- Anxiety disorder
  - Anxiety disorder due to... [indicate the general medical condition]
  - Anxiety disorder *Not Otherwise Specified* (NOS)

2.2.4 Encyclopedia of Stress

The Encyclopedia of Stress (Fink, 2007) is another inclusive and widely-used classification system for stress-related phenomena. This encyclopedia amalgamates hundreds of concepts under the subject categories of:

- Animal Studies and Models
- Conflict, War, and Terrorism
- Disasters
- Diurnal, Seasonal, and Ultradian Rhythms
- Drugs (Effects)
- Drugs (Treatment)
- General Concepts and Models

- Genetics and Genomics
- Human Cognition, Emotion, and Behaviour
- Human Health and Physical Illness
- Human Mental Health and Psychopathology
- Immunology, Infection, and Inflammation
- Laboratory Studies and Tests
- Therapies
- Physiological, Pharmacological, and Biochemical Aspects
- Psychological Therapy
- Psychosocial and Socioeconomic Aspects

This encyclopedia also provides explanatory articles, definitions, and related references for each introduced concept.

2.3 Ontologies in Biomedical, Medical, and Mental Health Sciences

Various domains of health, medical, and biomedical sciences have implemented ontology as an effective and operational tool for the management of their data and different communication purposes (Ceusters, Martens, Dhaen, & Terzic, 2001). Examples of such ontologies include: Gene Ontology (GO) (Gene Ontology Consortium, 2006), Unified Medical Language System (UMLS) (Lindberg, Humphreys, & McCray, 1993), Disease Ontology (DO) (Warren et al., 2006), and Haghighi-Koeda Mood Disorder Ontology (HK Ontology) (Haghighi, Koeda, Takai, & Tanaka, 2009). Recently, there have been several other proposals for the implementation of ontologies in the mental health domain, (e.g. Mental Health Ontology (MHO) (Hadzic, Chen, & Dillon, 2008)) to capture and organize information about different aspects of mental health such as the types of mental illnesses, their causes and treatments.

The following is a brief description of some of the established ontologies in the biomedical, medical, and health domains:

2.3.1 Gene Ontology (GO)

The Gene Ontology (GO) is a bioinformatics project, in the form of a controlled vocabulary of terms, which has been designed for the standardization of the informational representation of various types of genes and gene products contained in different databases. The information for the consistent description of gene product features and annotation data is obtained from GO Consortium members. The initial structure of this project in 1998 incorporated a collaborative amalgamation of three model organism databases of: the Saccharomyces Genome Database (SGD), the Mouse Genome Database (MGD), and FlyBase (Drosophila). Afterward, the GO Consortium was extended to integrate other databases of animal, microbial and plant genomes.

There are currently three ontologies implemented in the GO project to describe various categories of gene products with respect to their related *cellular components*, *molecular functions*, and *biological processes*. Such descriptions are general and inclusive, and are not constrained by specific species-dependent information.

2.3.2 Unified Medical Language System (UMLS)

The Unified Medical Language System (UMLS), designed by the US National Library of Medicine (Donald & Lindberg, 1986), is a collection of numerous controlled biomedical vocabularies which facilitate rapid access to and retrieval of relevant biomedical information and patient records, translation and mapping of various vocabularies, and implementation of natural language processing (Bodenreider, 2004).

The UMLS incorporates three major modules: Metathesaurus, Semantic Network, and SPECIALIST Lexicon. The Metathesaurus is the UMLS hub database comprised of approximately 100 controlled vocabularies and categorization systems (e.g. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10), *Medical Subject Headings* (MeSH), UK Clinical Terms, etc), over 1 million biomedical concepts, 5 million concept names, and many types of relationships between concepts. The

Semantic Network encompasses a set of semantic categories (semantic types such as *chemicals*, *organisms*, *biologic function*, *anatomical structures*, etc) and semantic relationships (hierarchical and non-hierarchical) which are utilized for the categorization and connection of the entries in the Metathesaurus. It contains 135 semantic types and 54 relationships. The SPECIALIST Lexicon is, in fact, a database of syntactic, morphological, and orthographic information about English vocabulary and other biomedical terms included in the UMLS Metathesaurus and MEDLINE. The Lexicon can be employed by a range of Java programs to analyse and link various forms of vocabulary which may appear in biomedical texts, thereby facilitating the process of Web searches. The UMLS also offers a number of supporting software tools such as *Knowledge Source Server* and *MetaMap* for different mapping and browsing purposes (Bodenreider, 2004).

2.3.3 Disease Ontology (DO)

The Disease Ontology (DO) (Warren et al., 2006) is an open source ontology which integrates biomedical data related to human disease. It can be considered as a disease-oriented subset of the UMLS which brings together numerous concepts associated with various types of disease (e.g. cancers, congenital abnormalities, deformities, and mental disorders) from UMLS Disease/Disorder semantic network and other medical resources. Compared to medical controlled vocabularies such as MeSH ("*Medical Subject Headings*," 2008), and *Online Mendelian Inheritance in Man* (OMIM) (Hamosh, Scott, Amberger, Bocchini, & McKusick, 2005), the Disease Ontology covers more general concepts about different dimensions of diseases. This enables more major classes to be recognised from their specific subclasses, thereby, increasing mapping accuracy (Osborne et al., 2009). Furthermore, the assignment of concepts about different heritable disorders to the context of other relevant diseases in the DO can enhance researchers' understanding of the states of diseases and create dynamic and evidence-based associations between various aspects of human disease (Warren et al., 2006).

2.3.4 Haghighi-Koeda Mood Disorder Ontology (HK ontology)

The Haghighi-Koeda Mood Disorder Ontology (HK Ontology) (Haghighi et al., 2009) is a recently established ontology in the psychiatry domain which covers both medical and psychological aspects of mood disorders. Serving both educational and clinical purposes, this ontology aims to enhance collaboration between psychologists and psychiatrists. For example, it can provide psychiatrists and clinical psychologists with different medical and psychological causes of a certain mood disorder, assisting them to make more effective decisions about treatment strategies.

The HK ontology incorporates a *knowledge base*, an *ontology search system* employed in the Web interface system, and the *HK Mood Disorder Diagnosis Scale*. The HK knowledge base forms an ontological tree of concepts pertinent to mood disorders. It includes 4 types of mood disorders and 9 criteria, 1160 terms and 620 term definitions. It also contains related references to each class node. The HK ontology search system is a Web interface system which can be used for keyword-based retrieval of information related to ontology concepts. Respectively, HK Mood Disorder Diagnosis Scale has a diagnostic function. It obtains information about the patient (based on the HK ontology) and provides the clinician with relevant information about the presence of a possible mood disorder.

The HK ontology is an OWL-based ontology which is formalized using Protégé 3.4 beta ontology editor (Haghighi et al., 2009).

2.4 Ontology Building Methods

In this section, we introduce a number of ontology-building methodologies which have been previously used by different ontologists and domain experts. These include: the *Knowledge Engineering Methodology* (Uschold & Gruninger, 1996), the *TOVE methodology* (Gruninger & Fox, 1995), *METHONTOLOGY* (Fernandez, Gomez-Perez, & Juristo, 1997), the *DILIGENT methodology* (Vrandecic, Pinto, Tempich, & Sure, 2005) and the *DOGMA* *methodology* (Spyns, Tang, & Meersman, 2008). In the following, we give a brief description of the abovementioned methods.

2.4.1 Knowledge Engineering Methodology

The Knowledge Engineering Methodology (Uschold & Gruninger, 1996) incorporates different stages of purpose and scope identification, ontology building (including ontology capture, coding, and integration), evaluation, documentation, as well as guidelines for each stage.

In the first stage, the ontology builder defines the reason for building the ontology and its intended applications. The ontology building stage includes different sub-phases of ontology capture, ontology coding, and integration of available ontologies. The ontology capture involves identification of the domain concepts, terms, and their relationships in addition to providing unequivocal definitions for those concepts and terms. In the coding sub-stage, a representation language will be selected to explicitly represent the captured conceptualization of the previous sub-stage. The integration task will consider the possible incorporation of other existing ontologies into our ontology.

In the next stage, the developed ontology is evaluated. The evaluation can be made with respect to reference criteria such as competency questions, requirement specifications, as well as compliance with the real world (Goméz-Pérez, Juristo, & Pazos, 1995).

The documentation stage addresses the documentation of all underlying assumptions about the concepts and their definitions in ontology in order to facilitate the process of effective knowledge sharing and reuse.

In the final stage, the ontology engineer elaborates on different methods and techniques which have been applied during the abovementioned stages (Uschold & Gruninger, 1996).

2.4.2 TOVE Methodology

The TOVE (TOronto Virtual Enterprise) methodology (Gruninger & Fox, 1995) aims to generate a common-sense enterprise model which is capable of deducing answers to users' implicit queries. It places a special stress on the formulation of informal competency questions to which the ontology must be an answer.

TOVE incorporates six stages: motivation scenario, informal competency questions, first-order logic: terminology, formal competency question, first-order logic: axioms, and completeness theorems.

In the motivation scenario stage, the ontology engineer identifies and describes situations and applications to which ontology is expected to offer solutions. The proposed motivation scenario also incorporates a number of intuitively potential solutions to the identified problems as well as a rationale for including certain objects in the ontology. In the next stage, the requirements or questions to which ontology should provide answers is specified and described in an informal way. Then, the informal competency questions are restated in ontology terminology which is formally expressed in first-order logic or KIF. The terminology specification relies on the identification of the objects, their attributes and relations in the intended knowledge domain. Then, in the next stage, the established ontology terminology is used to form the formal competency questions. Subsequently, through an iterative process, first-order logic axioms are defined in order to provide semantics for the ontology terms and concepts. Axioms provide terms with appropriate definitions and impose restrictions on their interpretations. The process of axiom specification is basically directed by the predefined formal competency questions. Axioms are necessary and must adequately express the competency questions and their potential solutions. If an insufficient number of axioms have been proposed, then they must be refined and extended, and if necessary, other axioms be added until there are adequate axioms for representing questions and solutions. In the final stage, called the *completeness theorem*, the expert will define the conditions under which the ontology has offered *complete* solutions to the competency questions. The completeness theorem can also be used as an index on the basis of which further extensions to the ontology will be evaluated. In fact, the formal competency questions, in this phase, are used to prove the completeness theorems of the established ontology (Gruninger & Fox, 1995).

2.4.3 METHONTOLOGY

Some methodologies such as METHONTOLOGY (Fernandez et al., 1997) offer an evolving prototyping life cycle concerning different aspects of the development of an ontology framework, support (e.g. evaluation and extension) of the ontology development, and related project management actions. The developmental process in METHONTOLOGY incorporates the stages of: requirement specification, domain conceptualization, formalization of the conceptual model in a formal language, implementation of the formal model, and maintenance of the implemented ontology. The support actions may include knowledge acquisition, documentation, evaluation, and integration of other ontologies. Finally, the project management activities concern the tasks of planning and control (Fernandez et al., 1997).

2.4.4 DILIGENT Methodology

The DILIGENT (Vrandecic et al., 2005) methodology is a methodology which aims to organize and manage Distribute, Loosely controlled, and evolvinG Engineering of oNTologies. It can be considered as an expansion of ontology engineering methodologies such as OnToKnowledge (Fensel, van Harmelen, & Horrocks, 1999) or Methontology with a special emphasis on user centrality. It also has special plans for the integration of automatic agents in the ontology evolution process, allowing the ontology engineer to adapt to the unremitting change of domain knowledge.

The process of ontology engineering in DILIGENT involves five major actions including: building, local adaptation, analysis, revision, and local update.

At the building stage, the initial ontology is built by a small number of domain experts, users, ontology engineers, and knowledge engineers. The ontology model at this stage need not be complete. After this preliminary ontology has been established, the users start working with it, developing their local ontologies by adapting it to their local requirements. The users are also able to modify the core ontology through a control board which records all modifications. Then, at the analysis stage, local ontologies and the requests for change are analysed by the control board so that similarities among them can be discovered. After that, decisions will be made as to which modifications need to be applied to the core ontology to meet various users' requirements. However, the new adaptations and localizations need to be revised in order to ensure the core ontology has not lost its sharable quality. Hence, the revision stage aims to adapt the ontology to various applicants' requirements, enhancing its acceptance, consensuality, and sharedness (Vrandecic et al., 2005).

Experts from different areas take responsibility for the revision of the ontology. For example, users evaluate the usability and advantages of the ontology, providing feedback to ontology engineers through their requests and requirements. Respectively, the existence of factual mistakes and the degree to which the ontology represents the intended knowledge domain are assessed by domain experts. Correspondingly, knowledge engineers and ontology engineers evaluate the technical dimensions of the ontology such as its efficiency, logical properties, or standard conformance, trying to update as well as hold the balance of different applied ontology modifications. Finally, at the stage of local update, applicants update their local ontologies to cope with the revisions which have been introduced to the modified core ontology (Vrandecic et al., 2005).

The DILIGENT methodology is particularly suitable for de-centralised knowledge management systems. It also offers flexibility in the use of ontology language or formalism (Vrandecic et al., 2005).

2.4.5 DOGMA Methodology

The DOGMA (*Developing Ontology-Grounded Methods and Applications*) (Spyns et al., 2008) methodology offers a special paradigm for separation of the domain axiomatization (the ontology base) from the application axiomatization (the commitment layer) with the purpose of finding a solution for the trade-off problem which often exists between an ontology's usability and its reusability. This advantage of DOGMA allows domain experts and users to have multiple views and requirements for different applications while using the same stored, meaning-independent conceptualization (Spyns et al., 2008). Moreover, the DOGMA proposes the notion of the context which can be considered as an identifier to restrict the interpretation of each term to the specified concepts which exist within the context of that term (Jarrar & Meersman, 2008).

2.5. Ontology Languages

In order to effectively build, apply, integrate, and evolve ontologies, we need to adopt a well-defined ontology language as well as effectual reasoning tools (Baader, Horrocks, & Sattler, 2004).

The aim of an ontology language is to offer the users a tool with which they can write conceptualizations of domain models in a formal and explicit fashion. To achieve this goal, an ontology language should have a well-defined syntax and semantics, effective reasoning support, ample expressive power, and expediency of expression (Antoniou & van Harmelen, 2004).

This section introduces the Web Ontology Language (OWL) and its preceding languages, i.e. Resource Description Framework (RDF) and Description Logics (DL), and explains the different aspects and capabilities of each language. The Web Ontology Language (OWL), which is the ontology language employed by the HSO to formalize its conceptualization, will be further explained and detailed in Chapter 7.

2.5.1 Resource Description Framework (RDF)

The Resource Description Framework (RDF) is defined as a *data model* which can be represented as simple *subject-predicate-object* triples (Bergman, 2009). It is a language recommended by W3C as the basis of the Semantic Web (Berners-Lee, Hendler, & Lassila, 2001) which aims to describe the Web page and non-Web page resources by defining named properties and their values. The vocabularies applied in the RDF descriptions are described by RDF Schema (RDFS) i.e. the RDF Vocabulary Description Language. Such vocabularies offer different descriptions of classes (concepts), their properties, and the relationships between those classes and properties. For example, ontological notions such as hierarchies of class and subclass, property and subproperty, or property domain and range can be described by RDF Schema. In other words, while the assertion of statements in the form of subject-predicate-object can be denoted by RDF, the description of such statements requires RDF Schema (Baader et al., 2004).

Unlike the traditional object-oriented and frame-based languages which are *resource (concept)-centric*, RDF is a *property-centric* language. Overall, a resource-centric language requires the ontologist to define concepts (resources) together with the possible properties of those concepts in a centralised method. This perspective does not allow a property to be defined independently of its respective underlying class. Therefore, the definition of a new property necessitates an earlier participation of a predefined class or creation of a new class for it. Conversely, a Web language such as RDF provides space for information and vocabularies to be described and represented in a decentralized mode. This initiative was inspired by the Web's capability of allowing anyone to create a new Web page and link it to other different Web pages. In a similar manner, RDF aims to provide its users with the potential to express anything they wish about everything. To do so, it offers the facility to define properties independently of the classes. As a result, the ontologist will be able to describe any class or resource with any already existing or added property/properties (Baader et al., 2004).

Overall, RDF is a language belonging to the cluster of Semantic Web languages. It has been established on the basis of *Uniform Resource Identifier* (URI) (Berners-Lee, Fielding, & Masinter, 1998) and *Extensible Markup Language* (XML) (Bray, Paoli, Sperberg-McQueen,

& Maler, 2000) languages. URI is the language of the Web which is used for naming entities. XML is the standard syntax used for the representation of information in the Web. Later extensions of RDF developed into ontology languages such as DAML+OIL (*DARPA Agent Markup Language* (DAML) + *Ontology Interchange Language* (OIL)) (Connolly et al., 2001) and OWL (Baader et al., 2004).

A directed graph can be used to represent RDF abstract syntax such that nodes represent resources (URIs) and arcs represent their properties (relationships). RDF specifies URIs for both resources and properties.

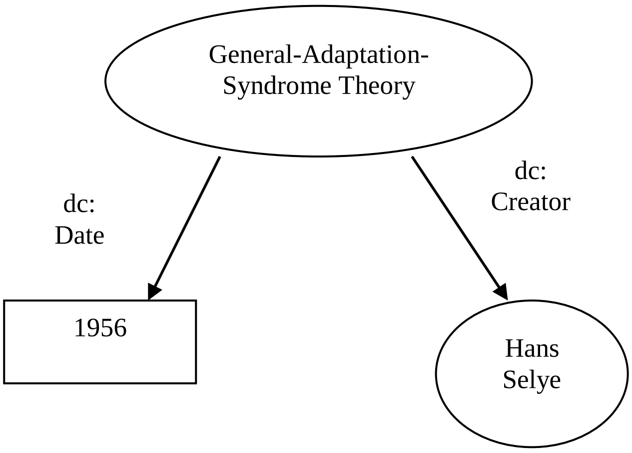

Figure 2.1. Example of a RDF graph

The above figure demonstrates a typical RDF graph in which each arc represents a *statement* in the following form: "`GeneralAdaptationSyndromeTheory hasDate 1956`", "`GeneralAdaptationSyndromeTheory hasCreator HansSelye`".

In the abovementioned example, the resource (General Adaptation Syndrome Theory) has two properties: *Date* with a value (1956), and *Creator* with a value (Hans Selye). In the RDF statements, the resource is called the *subject*, the property is called the *predicate*, and the value is called the *object* of the statement.

The modelling capabilities of RDF and RDFS enable vocabularies to be organised in typed hierarchies of subclass and sub-property relationships, operate domain and range restrictions, and define instance memberships. Nevertheless, they still lack some other significant features which can be used for the development of an ontology. These features tap into facilities for defining the *local* scope of properties (limiting range restrictions to some classes only), disjointedness of classes, cardinality restrictions, Boolean combinations of classes, and special characteristics of properties (such as transitivity, uniqueness, and inverse property) (Baader et al., 2004). Such drawbacks have been addressed by later ontology languages such as OWL.

2.5.2 Description Logics (DL)

Description Logics (DL) are a group of knowledge representation languages which can offer well-structured and formal representations of the knowledge of domains. Description logics can *describe* the significant ideas of one domain through concept *descriptions*. Such concept descriptions or expressions form concept and role combinations which incorporate atomic concepts (in the form of unary predicates) and atomic roles (in the form of binary predicates). Being equipped with formal and logic-based semantics, description logics are more advanced than *semantic network* or *frame*s (Baader et al., 2004).

Description logics employ Boolean constructors such as conjunction ($\cap$) (set intersection), disjunction ($\cup$) (set union), or negation ($\neg$) (set complement). They also adopt *existential restriction* constructors, the *value restriction* constructor, and the *number restriction* constructor.

Description logics can offer description formalism as well as terminological and assertional formalism. For example, terminological axioms can give names or abbreviations to complicated descriptions. Respectively, the properties of individuals can be expressed through assertional formalism (Baader et al., 2004).

2.5.2.1 Inference in Description Logics

The *inference* facilities of the description logics allow the user to infer implicit knowledge from the explicitly represented one. For example, the *subsumption algorithm* can deduce the superclass-subclass relationships (such that: *Y* subsumes *X* iff all instances of *X* are necessarily instances of *Y*). Or the *instance algorithm* can deduce instance relationships (such that: the individual *a* is considered to be an instance of the class description *X* iff *a* is always interpreted as an element of *X*). Moreover, the *consistency algorithm* can ensure the consistency and non-contradictory state of a knowledge base's assertions and terminological axioms.

However, it has been argued that a balance should be maintained between the expressiveness of the description logics and the complexity of its inference problems. The imposition of too severe constraints on concept descriptions may prevent some important notions of the domain from being expressed.

Description logics have been regarded as one of the best ontology languages as they are capable of offering formal semantics as well as reasoning tools. Such capabilities have made description logics the foundation for building Web ontology languages such as OIL, DAML+OIL, and OWL. Although there is an RDF Schema-based syntax for Web ontology languages, their design is based on one of the expressive description logics languages, DL *SHIQ* (Baader et al., 2004).

2.5.2.2 Description Logic *SHIQ*

The expressivity of SHIQ is due to its important features which make it an appropriate expressive ontology language. These features include: provision of more expressive number restrictions such as *qualified number restriction*, ability to formulate compound terminological axioms, and possibility of expressing *inverse roles*, *transitive roles*, and *subroles*. Further extensions of SHIQ may cover *concrete domains* or *concrete sets* by providing facilities for the modelling of concrete properties (e.g. real numbers, integers, or strings) of abstract entities (e.g. age, weight, or people's name) as well as comparison of such properties. They can also include *nominals* or concept names which are considered as s*ingleton sets* (Baader et al., 2004).

Given that *C* and *D* are SHIQ concepts, a finite set of *General Concept Inclusions* (GCI) *C* ⊆ *D* can be described as TBox[1]. Hence, an interpretation *I* can be a model of a TBox *T iff it satisfies all GCIs in T*. Therefore, we will have: $C^I \subseteq D^I$ for each *C* ⊆ *D* ∈ *T*. In *SHIQ*, we are able to reduce the *equivalence* relationship between two concepts to the *subsumption* one. In that case, we can say that two concepts *C* and *D* are equivalent (*C* ≡ *(R,T) D*) *Iff they subsume each other* (Baader et al., 2004).

SHIQ allows an ontology to be formalized in a TBox. To do so, one first needs to constrain the allowed interpretations in order to apply restrictions on the possible worlds (Baader et al., 2004). An example of such a restriction is when we aim to restrict our definition of *stress hormone* to either *Catecholamine* or *Glucocorticoid*. Using GCIs, we will have:

Stress Hormone ⊆ Catecholamine ∪ Glucocorticoid and Catecholamine ⊆ ¬ Glucocorticoid.

Therefore, a domain's basic notions (primitive concepts) can be axiomatized by GCIs, restricting statements of transitivity relations, as well as role inclusions. In the next stage, one can describe more complex notions (defined concepts) of the application domain by means of concept definitions. Also, SHIQ is able to compute the subsumption hierarchy of the defined concepts by means of a certain subsumption algorithm. The results of such a computation can then be represented in the form of a new TBox taxonomy. This new TBox taxonomy can be subject to further test and refinement. The knowledge engineer is able to check whether the defined concepts are desirable, satisfiable, and located in the right place of the taxonomy. Such expressivity and verifiability of the SHIQ-based taxonomies make SHIQ an effective language for ontology development (Baader et al., 2004).

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[1] In Description Logics, concepts and their relationships are split from instances and their roles (fact assertions). In this regard, the concept split or terminological knowledge which specifies the taxonomy of conceptual relationships in a domain is called the TBox, whereas the second split (i.e. assertions about the instances, individuals, and their roles) is known as the ABox (Bergman, 2010).

2.5.3 Web Ontology Language (OWL)

The limitations of RDF and RDF Schema as to the representation of some other ontology characteristics prompted researchers in the US and Europe to initiate the development of a more powerful ontology modelling language. In response to this need, a language called DAML+OIL (Patel-Schneider, Hayes, & Horrocks, 2003) was created as a joint project which incorporated the American proposal DAML-ONT (Stein, Connolly, & McGuinness, 2001; Hefflin, 2003) and the European language OIL (Fensel, van Harmelen, Horrocks, McGuinness, & Patel-Schneider, 2001). Later, DAML-OIL became the foundation on the basis of which W3C Web Ontology Working Group defined OWL as the standardized language of the Semantic Web (Antoniou & van Harmelen, 2004).

OWL is based on RDF and RDF Schema, and primarily employs RDF's XML syntax. However, to improve the readability of OWL documents, other syntactic forms such as a non-RDF-based XML syntax, an abstract syntax utilized in the language specification document, or a UML (Universal Modelling Language)-based graphical syntax may be adopted.

OWL documents (OWL ontologies) are RDF documents with the root element of `rdf: RDF` and some denoted namespaces. To start an OWL ontology, a number of house-keeping assertions can be made under an `OWL: Ontology` element, containing comments, version control, and notions about other included ontologies (Antoniou & van Harmelen, 2004). The *comment* assertion may appear in the following form:

```
<owl:Ontology rdf:about="http://www.hso.com/ontologies/hso.owl">
        <rdfs:comment>The Human Stress Ontology that conceptualizes and
represents knowledge about human stress.</rdfs:comment>
    </owl:Ontology>
```

Owl has taken a number of forms depending on the application and the complexity level for which it has been written. These include: OWL Full, OWL DL, and OWL Lite.

2.5.3.1 OWL Full

OWL Full can employ all the language constructors of OWL in any possible combination. However, the result of such combinations must comply with a legal RDF (Antoniou & van Harmelen, 2004).

2.5.3.2 OWL DL

An OWL DL-based ontology adopts a number of constraints so as it can benefit from the computational tractability of Description Logics. These constraints include:

- *Vocabulary Partitioning*
- *Explicit Typing*
- *Property Separation*
- *No Transitive Cardinality Restriction*
- *Restricted Anonymous Class*

The *vocabulary partitioning constraint* states that any resource can belong to only one of the language constructors of class, datatype, individual, object property, datatype property, data value, or the built-in vocabulary. Hence, no resource can be a member of two such constructors simultaneously.

Explicit typing asserts that the abovementioned vocabulary partitioning must be stated in an explicit fashion.

The notion of *property separation* offers further implications for having object properties and datatype properties disjoined. This means that one cannot define the characteristics of *inverse property*, *functional property*, *inverse functional property*, and *symmetric property* for datatype properties.

The restriction of *no transitive cardinality* states that transitive properties and their sub-properties cannot take any cardinality restriction.

The implication of *restricted anonymous classes* is that one can utilize anonymous classes only in the domain and range of `owl : equivalentClass` and `owl : disjointWith`, and in the range of `rdf : subClassOf` (Antoniou & van Harmelen, 2004).

2.5.3.3 OWL Lite

OWL Lite has adopted all the restrictions of OWL DL together with several other constraints such as:

1. Using the constructors: `owl : disjointWith`, `owl : Oneof`, `owl : complementOf`, `owl : hasValue`, and `owl : unionOf` are prohibited.

2. Cardinality declarations (i.e. minimal, maximal, and exact cardinality) can only take values of 0 or 1.

3. Domain and range of `owl : equivalentClass` must necessarily be a class identifier and not an anonymous class (Antoniou & van Harmelen, 2004).

Further description of the features and characteristics of OWL, which have been utilized in the HSO, is presented in Chapter 7. For a comprehensive list of OWL features, the reader can refer to related references (e.g. Horridge, 2009).

2.6 Ontology Tools

In order to formalize our ontology according to the desired ontology language, we need an ontology tool (ontology editor). Ontology tools are capable of translating a given conceptualization into a predefined formal ontology language in an organized and structured manner. They may also facilitate the process of concept browsing, reasoning, automatic classification, mapping, and present graphical visualizations of a domain conceptualization.

This section introduces a number of the ontology tools used by different enterprises and describes some of their characteristics. Further elaboration on different features of the Protégé 4, the ontology tool employed for the formal representation of the HSO, is covered by Chapter 7.

There are a number of ontology tools available, each with common and specific characteristics. Some of the widely used ontology tools include: Apelon DTS (Distributed Terminology System), DOGMA tool, and Protégé tool.

2.6.1 Apelon DTS (Distributed Terminology System)

The *Apelon DTS* (Distributed Terminology System) ("*Apelon Distributed Terminology Server (DTS)*",1999) integrates a set of open source elements in order to supply inclusive terminology facilities for disperse applications. In particular, Apelon DTS is applied in situations where activities such as clinical data entry, administrative review, decision support, and information retrieval are required. It is also able to visualize the ontology concept graphs.

2.6.2. DOGMA Tool

The DOGMA tool provides the user with the capability of storing basic concepts and their application-specific constraints in two separate layers which form the *ontology base* and the *commitment layer* correspondingly. The ontology base incorporates *lexons* which are formal representations of basic concepts and their relationships in the form of *<Y: trem1 role1 co-role2 term2>*. Additional constraints on the lexons can be defined separately in the application or commitment layer, allowing users to have multiple perspectives and applications for the same conceptualization (Jarrar & Meersman, 2008; Spyns et al., 2008).

2.6.3. Protégé Tool

Protégé tool (Noy, Ferguson, & Musen, 2000) is an OWL-based updating ontology-building tool which is widely used by various communities (Dean et al., 2003). Protégé offers various visualizing, browsing, and reasoning facilities which make it one of the best ontology editors in this regard. It also provides the users with different tabs such as active ontology tab, classes tab, properties tab, as well as class description and metadata views which facilitate the process of concept definition and description. Protégé allows free download and publishes updated practical guides for the users (Horridge, 2009). Further details about this tool are provided in Chapter 7.

2.7 Previous Attempts to Refine and Evolve Ontology Relationships

Ontology evolution can be defined as the well-timed adjustment of ontology to the encountered alterations as well as the consistent management of those alterations (Haase & Stojanovic, 2005). Such alterations may be due to a number of factors such as the occurrence of change or conflicts in the goals, needs, and perspectives of domain experts or ontology users (De Leenheer & Mens, 2008), discovery of new knowledge in the domain, or change in the original conceptualization (Flouris & Plexousakis, 2005).

Researchers have proposed a number of ontology refinement and evolution strategies to address the encountered conflicts and maintain the consistency of ontology. In the following, we present a brief review of some of the significant directions and research orientations which deal with the problem of ontology evolution across various domains.

2.7.1 User-driven Ontology Evolution Management

Stojanovic, Maedche, Motik, and Stojanovic (2002) propose a six-phase ontology evolution process to analyse the causes and effects of the occurred changes and maintain the consistency of ontology in a systematic manner. The proposed evolution process consists of the stages of: change capturing, change representation, semantics of change, change implementation, change propagation, and validation.

In the first stage, i.e. change capturing, the encountered changes in the domain conceptualization or users' needs are identified and captured.

In the next stage, i.e. change representation, the identified changes must be applied and represented in an appropriate format. For example, we can represent and perform the required concept addition (e.g. Add-Concept-X) or concept deletion (e.g. Delete-Concept-Y) according to a given format in the ontology. The required changes might be of a composite nature (e.g. Merge-Concepts) which entails an appropriate representation format.

The applied changes in the previous stage are likely to bring about a number of inconsistencies in other sections of the ontology which need to be dealt with. For example, removal of a concept and its related property may result in ambiguity in the semantics of its remaining sub-concepts. The third stage of ontology evolution, i.e. semantics of change, attempts to resolve such induced and contingent alterations, trying to maintain the consistency of the ontology in a systematic way. One of the disambiguating methods which can be implemented in this regard is to add meta-information describing the semantic role of each ontology entity and their properties.

In the fourth stage, the required changes are applied to the ontology. The suggested changes, however, need to be checked and approved by the ontology user before being implemented.

The implemented changes, in the fifth stage, are propagated to other related parts of the ontology to maintain its consistency as a whole. For example, the concept modifications are propagated to ontology *instances* of the modified ontology as well as other dependent ontologies and applications which function based on that ontology.

Finally, to allow flexibility for reversing and undoing the effects of ontology evolution, the validation stage is provided. Using evolution logs, the user is able to track information about the occurred modifications in the ontology and their consequent outcomes. Evolution logs also offer meta-information about the type of changes, their costs, time, causes, and identity of their authors. At this stage, users may also implement different tools and strategies such as data mining algorithms to analyse patterns of ontology use and refine ontology content and structure accordingly (Stojanovic et al., 2002).

2.7.2 Belief Change-based Ontology Evolution

2.7.2.1 Belief Change

Belief change (*belief revision*) refers to the process of altering beliefs in an agent in order to incorporate emerging information. Belief change strategies and algorithms offer the most rational methods of managing the incoming alterations in the agent's knowledge base. In this sense, unlike knowledge representation which handles the representation of the static features of knowledge, belief change seeks to manage the dynamic and evolving facets of knowledge (Flouris, 2006; Flouris & Plexousakis, 2005).

Belief change may apply different strategies in order to cope with the appearance of new knowledge about the domain or alteration of the domain realities (Flouris & Plexousakis, 2005). Overall, three strategies can be adopted when the domain is static, but our knowledge of the domain changes due to the emergence of a new piece of information. These include *expansion*, *revision*, and *contraction* (Alchourrón, Gärdenfors, & Makinson, 1985).

Expansion refers to the reckless addition of the new information into the knowledge base, regardless of whether or not the newly added information will result in an inconsistency in the knowledge base; whereas, revision implies the process of inserting a new piece of information into the knowledge without producing any inconsistency. To achieve this, one might have to abandon some of the old beliefs which contradict the new information. Subsequently, contraction refers to the process of consistent removal of unreliable information from the knowledge base (Flouris & Plexousakis, 2005).

On the other hand, when the real world (domain) changes, the knowledge base has to adjust to the new reality. In such dynamic scenarios, the strategies of *update* and *erasure* are suggested to change the knowledge base according to the new alterations in the domain. The update operation, similar to revision, refers to the addition of new information; while the erasure operation, like contraction, eliminates information from the knowledge base (Flouris & Plexousakis, 2005; Katsuno & Mendelzon, 1991).

2.7.2.2 An Ontology Evolution Strategy Based on Belief Change Techniques

Flouris and Plexousakis (2005) have proposed the incorporation of belief change techniques to automate the process of ontology evolution, excluding the role of human users from the cycle of ontology evolution. Ontology, in their approach, is represented as "*a set of DL [Description Logic] axioms*" (Flouris & Plexousakis, 2005), facilitating the migration of belief change strategies to the DL framework, thereby, presenting a unifying method for the management of different types of ontology alterations (Flouris & Plexousakis, 2005).

In the same manner, it is proposed that ontology changes be represented as a set of DL axioms. In this way, four types of ontology evolution operations, inspired by belief change operations, can be implemented to evolve domain ontologies. These include: *ontology revision*, *ontology contraction*, *ontology update*, and *ontology erasure*. Such ontology operations represent different types of change in an ontology. Hence, the process of ontology revision incorporates a new piece of information into an ontology which represents a static world. Likewise, ontology contraction refers to the process of eliminating a piece of information from an ontology which corresponds to a static world. Alternatively, ontology update refers to the incorporation of a new piece of knowledge into an ontology which represents a dynamic world; whereas, ontology erasure removes some information from an ontology which symbolizes a dynamic world (Flouris & Plexousakis, 2005).

In other words, ontology revision and contraction require us to incorporate our new knowledge and observations of an unchanged static world into the ontology conceptualization; while ontology update and erasure entail the adaption of our conceptualization to the occurred changes in a dynamic world (Flouris & Plexousakis, 2005).

Different algorithms have been suggested to deal with the incorporation of new domain information into the ontology or removal of some ontology statements. For example, through the process of *weakening of the original ontology* (Flouris & Plexousakis, 2005) we may be able to add new seemingly contradictory information to the ontology without causing a state of inconsistency. In this case, addition of an exception rule to an original ontology axiom (belief) can weaken the strictness of that axiom, providing space for the incorporation of other relevant, yet contradictory, statements (Flouris & Plexousakis, 2005).

The described ontology evolution strategy begins with the observation of a new fact or data which entails a corresponding ontology evolution or adaptation. The type of observation (e.g. change of real word or discovery of contradiction in our conceptualzaion) is identified by an ontology engineer or some type of sensor. Then, in the next stage, the required change operation (e.g. revision, update, etc) is determined, represented, and fed into the system through the implementaiton of a given algorithm. Subsequently, the required changes are performed automatically across the ontology. In this way, an automatic or semi-automatic and formal treatment of ontology evlution can be achieved (Flouris & Plexousakis, 2005).

2.7.3 Probabilistic-based Ontology Evolution

It has been noticed that ontology evolution has to cope with incomplete and uncertain information (Scharrenbach, 2008). To manage probabilistic uncertainty of ontological statements, there have been some efforts (e.g. Ding & Peng, 2004; Lukasiewicz, 2007; Lukasiewicz & Straccia, 2008) to equip Description Logics (DL) and OWL language with probabilistic extensions. For example, the *Probabilistic Description Logics* (PDL) is an extension of DL proposed by Lukasiewicz (2007) to assign conditional probability constraints to individuals and concepts in DL-based ontologies. Likewise, FuzzyOWL (Straccia, 2005) was introduced to enable the modeling of fuzzy concepts and roles in OWL-baed knowledge bases. The resultant explicit modelling of incompleteness and uncertainty allows the ontology developers to express probabilistic knowledge (Bacchus, 1990) such as "the probability that the administering of Clomipramine will treat Obsessive Compulsive Disorder is 0.5[2]".

In PDL, a conditional probability constraint ($\psi \mid \phi$) [l, u] indicates that given evidence ϕ, the probability that ψ can be concluded ranges between l and u. Likewise, a probabilistic class assertion ($\phi(o) \mid \top$) [l, u] means that individual o is a member of class ϕ with a minimum probability of l and maximum probability of u (Scharrenbach & Bernstein, 2009).

Using PDL, Scharrenbach and Bernstein (2009) propose a strategy which automatically deals with the occurrence of inconsistencies in the process of ontology evolution. Inconsistency occurs when a new piece of information, which contradicts a general ontological statement, is added to ontology (Scharrenbach & Bernstein, 2009).

The proposed strategy by Scharrenbach and Bernstein employs defaults in PDL to manage inconsistency occurring within an ontology. The following example illustrates this strategy. Suppose that the TBox: T= {PP $\subseteq$ GAD, GAD $\subseteq$ HC} implies that all PTSD[3] Patients (PP) have also Generalized Anxiety Disorder (GAD), and patients with Generalized Anxiety Disorder are also patients with Hypercortisolemia (HC). However, a new piece of information indicates that PTSD patients do not suffer from Hypercortisolemia, which can be illustrated as PP $\subseteq$ $\neg$HC.

Addition of this new information causes inconsistency in the TBox. To resolve this inconsistency, we can delete the most general pieces of information from the TBox and turn them into the defaults: (HC | GAD) [1, 1] and ($\neg$HC | GAD) [1, 1]. These defaults are then inserted into the new PTBox (Probabilistic TBox). In this way, the most general information, i.e. T= {PP $\subseteq$ GAD, GAD $\subseteq$ HC}, is relaxed and reduced to the abovementioned defaults, resolving the observed inconsistency within the ontology (Scharrenbach & Bernstein, 2009).

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[2] The mention of 0.5 probability is for example purposes only.

[3] Post-Traumatic Stress Disorder

2.7.4 Realistic Evolution of Scientific Ontologies

Smith and Ceusters (2010) propose a *realist methodology* for the evolution of ontologies based on the theory that ontologies are "*representations of the reality that is described by science*" (Smith & Ceusters, 2010). The realist methodology taps into the *metaphysical realism* which presumes the existence of *universals* or *types*[4] in the real world. Analogous to the strategies adopted by the international system of units to standardize physical measurements, the realist methodology aims to ensure that concepts (general terms) in scientific ontologies correspond to the universals in reality (Smith & Ceusters, 2010).

The outcome of this objective is the development of *reference ontologies*. A reference ontology in a scientific domain incorporates the reality-based concepts of that domain and the relationships between them (i.e. scientific laws), representing the scientific evidences discovered by that domain. By using it as a reference point, ontology developers in a domain can ensure the upper-level architecture of their newly developed ontologies is consistent with the already established facts asserted by the reference ontology (Smith & Ceusters, 2010).

The realist ontology evolution methodology is described within the framework of a scientific annotation strategy which aims to ensure the annotation consistency among the administrators, and promote the development and evolution of reference ontologies for biomedical domains (Hill, Smith, McAndrews-Hill, & Blake, 2008). The proposed annotation process includes the following stages:

1. Relevant experimental data which are embedded in scientific literature are identified by the administrator.

2. With the help of expert knowledge, the administrator determines and extracts the appropriate general terms, i.e. those referring to the discovered universals or types, from the results of the experimental data. Conversely, the inappropriate general terms which have no counterparts in reality will be omitted from the collection.

[4] Universal or types are the real-world equivalents of the *general terms* adopted by scientific theories to describe natural laws, i.e. repeatable aspects of the real world (Smith & Ceusters, 2010).

3. Based on the extracted general terms and the ontology concepts in the reference ontology, the administrator creates appropriate annotations which connect the extracted terms to their corresponding ontology types (concepts). These annotations are, then, transferred to an annotation database.

4. In cases where the reference ontology does not include or misclassify a certain representative concept required for annotation, a request is submitted by the administrator calling for inclusion or correction of that concept in the ontology. Respectively, those ontology concepts that do not represent any discovered universal in the experimental data are removed from the ontology. In this way, the evolution of the reference ontology is grounded in the feedback received from the ontology users who apply the ontology for annotation purposes (Hill et al., 2008; Smith & Ceusters, 2010).

2.8 Critical Review of Literature

2.8.1 Critical Review of Previous Attempts to Classify Stress-related Concepts

With the advent of computer systems, previous manual strategies for the retrieval of stress-related data, e.g. Selye's Symbolic Short-hand System for Medicine and Physiology, have become outdated (Everly & Lating, 2002) since manual systems of classification are not able to process, retrieve, or analyse information in an automated and accelerated way. Furthermore, since the early work of Selye, knowledge about human stress has dramatically increased. As a result, it is not tenable to incorporate the limited categorization of Selye's system into the multidimensional classification system of the HSO.

Considering the amalgamation and organization of knowledge about various aspects of human stress, classification systems such as categorization of coping strategies and DSM-IV offer a limited view of stress-related knowledge. For example, Ryan-Wenger' (1992) classification system for children coping strategies is limited to conceptualization and description of coping strategies adopted by children in different age groups. Respectively, DSM-IV presents information about the psychopathological aspects of human stress, but not sufficiently elaborating on other relevant social or biological dimensions. In this regard, incorporation of the MeSH mental disorders category into the HSO has spontaneously covered most of the stress-related categories of the DSM since MeSH comprises the majority of the DSM categories.

Furthermore, previous classification systems in stress domain do not allow for the intelligent search and retrieval of desirable information.

Endeavours such as the encyclopedia of stress offer an inclusive coverage of most stress-related concepts and related information about them. The encyclopedia of stress (Fink, 2007) presents revised and updated articles concerning the latest advances of knowledge about various physiological, neurophysiologic, and psycho-social aspects of stress. It also provides the users with flexible navigation facilities such as online searching, browsing, and internal cross-referencing between its articles which can be accessed via the ScienceDirect ("*ScienceDirect*," 2010) website. There are also links to related articles and related reference works for each article title of the encyclopedia.

However, despite such facilities, the encyclopedia of stress fails to present an interrelated model of stress-related concepts or to demonstrate the links between them. This lack of an ontological organization and formalization for the diversity of incorporated concepts and theories in the encyclopedia of stress has resulted in difficulties tracking the possible links and interrelations between various concepts. This, in turn, has prevented the effective and intelligent retrieval and analyses of stress-related information.

For example, an individual searching for a particular concept e.g. *Buspirone* in the encyclopedia of stress, is less likely to find it and its related concepts by looking at the alphabetical headings in the table of contents; whereas, using the HSO, he/she will be able to retrieve it automatically under its superclass category, *Pharmacologic Medication*, which is located under the category of *Pharmacotherapy*. Hence, the HSO has the ability to demonstrate the associations between a particular concept and many other concepts and theories, describing it as an interconnected element of a network of interwoven concepts in the form of an ontological model of human stress.

We have incorporated many stress-related concepts of the encyclopedia in the HSO. However, we did not use the subject headings of the encyclopedia for our high-level categories since they do not fit into the HSO interconnected model of stress knowledge. For example, the subject headings of Conflict, War, Terrorism, and Diurnal, Seasonal and Ultradian Rhythms in the encyclopedia represent only a few sub-concepts of the high-level categories of Stress Cause and Stress Mediator in the HSO.

In this respect, further extensions of the HSO can include and formalize all stress-related concepts embedded in the encyclopedia, and illustrate their possible inter-associations in one framework, thereby enabling automated programs to intelligently analyse and retrieve desirable information.

Therefore, in comparison to previous efforts, we propose that the HSO is likely to produce a more effective, convenient, and practical repository of information for stress researchers and clinicians.

2.8.2 Critical Review of Previous Ontologies in Health and Medical Domains

Overall, biomedical ontologies such as Gene Ontology (GO) rarely include any particular information about human stress.

The Unified Medical Language System (UMLS) incorporates a multitude of medical concepts within which there exist many stress-related concepts and terms. The included categorization systems such as MeSH and ICD-10 in UMLS metathesaurus provide the user with definitions and taxonomical relationships between various medical concepts. Respectively, the UMLS semantic network incorporates both hierarchical and non-hierarchical relationship types between semantic types. However, its non-hierarchical relationship types are limited to five key categories: “physically related to”, “spatially related to”, “temporally related to”, “functionally related to”, and “conceptually related to”.

Although the UMLS constitutes a repository of many stress-related concepts, it has not been designed for the organization and management of stress-related data in particular. As a result, it lacks many relevant concepts related to social and psychological aspects of human stress. Furthermore, the relationship types in its semantic network do not cover the richness of relationships and theories in the domain of human stress as are represented by the HSO. Therefore, the UMLS can be used only as a reference resource for the building of more specific stress-related ontologies such as the HSO.

Likewise, ontologies such as Disease Ontology and Haghighi-Koeda Mood Disorder Ontology have not been developed for the organization, conceptualization, or effective analysis of stress-related knowledge, although they incorporate many stress-related concepts. Nevertheless, the Haghighi-Koeda Mood Disorder Ontology is of particular importance since it is one of the rarest established ontologies in the psychology and psychiatry domains and it covers both the psychological and psychiatric aspects of mood disorders.

By and large, current ontologies in health and medical domains do not fulfill the need for the establishment of a specific stress-related ontology. The HSO was developed as a response to this need.

2.8.3 Critical Review of Ontology Building Methods, Languages, and Tools

The abovementioned ontology-building methods have basic commonalities with respect to different stages of purpose identification, domain conceptualization, formalization, and evaluation of ontology. However, some methodologies offer supplementary stages in order to fulfil certain requirements and be effective in different applications. For example, the TOVE methodology proposes the early incorporation of informal competency questions as an evaluation criterion for the effectiveness and completeness of the designed ontology. Respectively, METHONTOLOGY focuses on the maintenance and evolution of the ontology. Likewise, the DILIGENT methodology focuses on user centrality and highlights the need to adapt the established ontology to its applicants' requirements. Likewise, the DOGMA methodology separates the domain axiomatization (the ontology base) from the application axiomatization (the commitment layer) in order to provide space for both ontology specific applications and their reusability.

For the design of the HSO, we have incorporated the basic stages of the Knowledge Engineering Methodology plus other notions from DOGMA methodology. For example, we adopted the stages of vision statement, conceptualization of domain knowledge, formalization of the conceptualization, and evaluation from the Knowledge Engineering Methodology, and used the notions of identification of knowledge resources and text selection from DOGMA methodology.

In developing our ontology, we have not included informal competency questions or adaptation to users' needs, as are proposed by some methodologies. Indeed, this primary version of the HSO has focused mainly on the organization of stress-related data and coverage of the concepts and theories in the stress domain. However, further refinement and evolution of the HSO could consider issues such as definition of competency questions and adaptation of the ontology to various communities of users.

Regarding the ontology language, the HSO has employed OWL as it is more advanced than its preceding languages, has incorporated both RDF and description logics, and more importantly, is the standardized language of the Semantic Web. Moreover, OWL is the language used by most prominent ontology editors such as Protégé.

Concerning the ontology tools, we have used the Protégé tool considering its utilization of OWL language, commonality, inclusiveness, powerful visualizing and reasoning facilities, and access to its standard and updating practical guides. The protégé tool provides more flexible visualization facilities compared to DOGMA or Apelon DTS tools. It also allows different metadata types for concepts and axioms to be created.

2.8.4 Critical Review of Attempts to Refine and Evolve Ontology Relationships

The user-driven ontology evolution strategy allows users to control and customize the ontology evolution process according to their needs and conditions. It also allows them to add metadata to concepts and their properties, explaining their meaning or role in different contexts in which they appear (Stojanovic et al., 2002). However, this strategy does not offer any solution for the dynamic and automatic evolution of ontological relationships in scientific domains.

The belief change-based ontology evolution offers some rational methods for handling dynamic features of knowledge as well as capturing dynamic changes in the real world. By representing changes in the form of ontological axioms, it also dispenses with the need for defining complex operators for each type of encountered alteration. Another advantage of this strategy is its ability to automatically evolve ontologies particularly in situations where the ontology users are not able to manage a multitude of encountered changes. However, this method requires all changes to be represented in the format of DL axioms, not being able to express those changes that are not expressible via the DL formalizations (Flouris & Plexousakis, 2005). Furthermore, it does not offer a reliable mathematical framework for the examination and manipulation of the evidence obtained from scientific works.

The probabilistic-based ontology evolution, based on the PDL, offers a solution for the representation of and reasoning with uncertain and incomplete knowledge. Furthermore, the PDL makes use of defaults for OWL ontologies in order to resolve the inconsistencies that occur during the process of ontology evolution (Scharrenbach & Bernstein, 2009). However, this approach does not offer any solution for the evolution and refinement of ontology relationships based on scientific evidence. Nevertheless, the framework proposed for the representation of uncertain information can be applied to our future work to improve the representational framework of the EBEO methodology.

The approach of ontological realism (Smith & Ceusters, 2010) supports our purpose of grounding ontological relationships in the evidence, purportedly representing the real world. However, the proposed methodology does not implement any automatic strategy for the dynamic refinement of ontological relationships. In this respect, the EBEO approach can be considered as a solution for the automatization of the realist ontology perspective.

Finally, to the best of our knowledge, currently no ontology evolution methodology exists which addresses the continually changing relationships between concepts in scientific ontologies in an automatic and evidence-based manner. The development of reliable, effective, and evidence-based ontologies for the scientific domains entails the establishment of evidentiary (in addition to consensual) relationships between concepts with the capacity to adjust and evolve in response to new incoming research results and contributions.

2.9 Conclusion

We described some of the previous categorization systems in the domain of stress such as the DSM-IV and the Encyclopedia of Stress. We also explained some of the previously established ontologies in health and biomedical domains. Recently, the application of ontologies in psychiatry and psychology domains has been proposed by some researchers. Nevertheless, it was emphasized that none of the preceding stress classification systems, data repositories, or ontologies has managed to establish a specific ontological framework for stress-related concepts and theories.

This chapter also elaborated on some of the ontology-building methods, ontology languages, and ontology-building tools. We mentioned that our methodology adopted the basic stages of ontology development from different methodologies such as the Knowledge Engineering Methodology and DOGMA method. Respectively, our choice of the OWL language and Protégé tool was based on their commonality, flexibility, effectiveness, and the standard state across various health and biomedical communities.

Finally, we provided an overview of some of the previous efforts to refine and modulate ontology relationships. Despite various advantages of each method, almost none of them have offered an automatic strategy for the evidence-based evolution and representation of ontology relationships in scientific ontologies. There is a need to find a solution to this issue. In the next chapter, we elaborate on the research issues which have been addressed by this thesis.

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Chapter 3 –Research Issues

3.1 Introduction

The results of various research works on the multidimensional concept of stress have been stored in diverse medical, psychiatry, and psychology information resources. However, the multiplicity and dispersion of such information have caused a number of problems and issues in the stress research to which the HSO aims to offer some practical solutions. After defining some of the key concepts which appear throughout this thesis, this chapter outlines the research problems we aim to resolve. We also draw on some of the issues resulting from the specified problems and explain how the choice of ontology can be regarded as a potential solution to those problems and issues.

3.2 Concept Definition

In order to avoid ambiguity, we define some of the most important concepts used in this thesis as follows:

- ***Stress***

Stress in this thesis is defined as the *organism's adaptive physiological, cognitive and behavioural responses to challenging and harmful conditions* (Monroe, 2008).

- ***Conceptualization*:**

Conceptualization includes the *identification of a domain's concepts and the relationships between them for which we propose a knowledge model* (Noy & Hafner, 1997).

- ***Formalization***

Formalization refers to the *process of establishing explicit and computer-readable definitions and descriptions for the concepts in a knowledge model* (Studer, Benjamins, & Fensel, 1998).

- ***Ontology***

Gruber (1993) defines ontology as a "*formal, explicit specification of a shared conceptualization*".

Ontology in this thesis is defined as a *machine-readable and human-understandable conceptualization and classification of the knowledge of a domain which is composed of the domain concepts and the relationships between them* (Guarino & Giaretta, 1995).

3.3 Problem Definition

The main problems this thesis aims to resolve are:

3.3.1 Lack of a Formal Conceptualization Framework for the Description, Organization, and Classification of Stress-related Information

Despite the previous attempts to develop different classification systems, taxonomy, or encyclopedia for stress knowledge, there was no organized formal framework for the conceptualization and classification of stress-related information. This lack of a formal computer-readable framework has hindered the process of effective search of stress-related concepts.

The development of an ontological framework can offer a formal conceptualization framework within which all stress-related information can be conceptualized, described, classified, and placed under their relevant categories. To resolve this problem, this thesis aims to:

design a semi-formal conceptualization framework for the description, organization, and classification of stress-related information.

3.3.2 Lack of an Ontology Evolution Methodology for Automatic/Evidence-based Refinement of Ontological Relationships

Notwithstanding the prominent emphasis on the consensuality of ontology (Compton & Jansen, 1990), in scientific domains it is also desirable to consider the correspondence of ontology relationships to real physical relations in the nature. This perspective holds that high-quality ontologies are the ones that represent the reality and include universals that exist in the real world of space and time (Smith, 2004). Hence, the incorporation of reality-based concepts and their relationships in an ontological framework such as the HSO entails the preparation and inclusion of accurate and evidence-based facts which are obtained from research literatures.

Nevertheless, the task of defining evidence-based ontological relationships (particularly operational ones) is complex and difficult. For example, as we experienced with the HSO, it is not reasonable to establish a certain operational relationship between two concepts based on a single research report or conclusion. Moreover, relationships in theoretical statements tend to change or evolve with time as new research results emerge in the domain of interest. For this reason, it is important to have a systematic strategy for the establishment of evidence-based ontology relationships which can also evolve in line with the evolving research results.

However, despite this need, there is no ontology evolution methodology which addresses, in a systematic evidence-based fashion, the dynamic change in relationships between concepts in scientific ontologies such as the HSO. To address this issue, we need to equip our ontology with the capacity to evolve and change its relationships in accordance with the incoming evidences from scientific literature.

To resolve this problem, this thesis aims to:

design an ontology evolution strategy which establishes evidence-based ontology relationships between the concepts in scientific ontologies in an automatic manner.

3.4 Research Issues

We have also identified the following research issues in the domain of human stress which have resulted from the first abovementioned problem.

3.4.1 Lack of an Inclusive Subject-based Classification System for Stress-related Concepts

Although there exist a small number of subject-based manuals or classification systems (e.g. DSM (American Psychiatric Association, 2000) or classification of coping strategies (Ryan-Wenger, 1992)) for the organization of stress-related phenomena, there is no inclusive subject-based information resource which incorporates all stress-related phenomena. Current manuals or encyclopedias are either limited to a few stress-related topics (e.g. stress-related disorders) or do not present subject-based categorization systems (e.g. in case of the Encyclopedia of Stress (Fink, 2007)).

Often researchers or clinicians want to obtain inclusive information about one particular stress-related subject such as the mediating role of cognitive and emotional factors in stress response. Using current information resources, encyclopedias, or clinical manuals, it is hardly likely that one will find all aspects of *cognitive mediators* and *emotional mediators* in one place. Therefore, we need an inclusive subject-based information framework which brings together as much information as possible under the predefined and specific subjects of stress such as cognitive or emotional mediators, thereby, saving researchers' time and effort.

3.4.2 Difficulty in Viewing Links and Interconnections between Stress-related Phenomena

There are numerous concepts, categories, theories, and results from various studies contained in different electronic journals and texts which are stored within a large number of information resources. However, stress-related findings appear to be fragmented and lacking in cohesion, especially regarding research into stress conducted within the domain of psychology (Hunt, 2005). Knowledge and data are often exclusively accumulated by some theorists to strengthen their point regardless of the existence of opposing data in the works of other theorists (Hilgard, 1987), or the fact that competing theories can be valid in different contexts (Bitterman, 1967; Mitchell, 2003).

Of fundamental value in research are the potential relations our data have with multiplicities of other theories and methods which have elaborated on different aspects of the same or relevant phenomena (Hunt, 2005). However, current classification systems or encyclopedia in the field of stress do not offer an inclusive view of links and interconnections between different stress-related concepts or topics. This has led to difficulties in obtaining an integrated view of stress knowledge.

Despite such problems within the field of human stress research, to the best of our knowledge, there has been no attempt to establish an ontology for human stress and its related concepts. Hence the need to establish the human stress ontology (HSO).

3.4.3 Data Heterogeneity and Autonomy of Information Resources within the Human Stress Domain

Despite the plethora of concepts, categories, theories, and research results contained in various electronic journals and stored within numerous information resources, most of these information resources function autonomously. It means contents in certain information resources are developed, stored and processed in isolation and independently from other information resources. This autonomy has caused different information resources to have different contents and dissimilar formats for information storage. The data are also stored heterogeneously. This prevents agents and search engines from understanding, analysing, and eliciting in a precise and integrative manner the desired information embedded within various databases.

Overall, there are three types of data heterogeneity in data sources: syntactic heterogeneity, schema heterogeneity, and semantic heterogeneity (Bishr, 1998). Syntactic heterogeneity is a result of using different representation languages or models. Schematic heterogeneity is caused by structural dissimilarities. Semantic heterogeneity results from lack of common meaning and understanding of the data amongst the agents (Cruz & Xiao, 2005).

The invention of XML (Extensible Markup Language)[1] (W3C, 2008) made the task of syntactic integration possible. However, it was not able to resolve the issues of semantic and schematic data heterogeneity. Therefore, ontologies were introduced as effective tools to facilitate the process of semantic and schematic data integration.

Here we must mention that the purpose of this thesis at this stage is not to solve the issue of data heterogeneity and autonomy of information resources in the stress domain. However, further development of the HSO in the future has the potential to address these issues.

[1] Extensible Markup Language (XML) is a syntactic structure consisting of a set of rules which encode Web documents in a machine-readable form (W3C, 2008).

3.4.4 Difficulty in Retrieval of Desirable Information through Current Search Engines

The current heterogeneity of data has made it difficult to devise search engines capable of performing simultaneous search and retrieval of relevant information from various information resources (Hadzic et al. 2009).

One of the most fundamental obstacles researchers face in the process of performing effective research works, literature reviews, and systematic reviews is the complexity and difficulty of information retrieval and analysis of relevant and desirable information. Research in the stress domain is no exception. Anyone searching for a particular stress-related concept or theory has to go through a huge bulk of literature embedded in a diverse range of text or electronic resources.

Moreover, effective and efficient retrieval of particular information from one single information resource through a key-word based search engine is a difficult, if not impossible, process. For example, a search for the term *psychological stressors* in the OvidSP database generates more than 17000 results. This diversity of results, by nature, incorporates both relevant and irrelevant data from various research works.

Such a widespread compilation of data about psychological stressors is highly unlikely to offer associations, interrelations, similarities and differences between related concepts and theories albeit most of those studies have investigated the same phenomenon, shared many theory elements and conceptual constructs with each other, or are in many cases either explanatory or contradictory to one another.

Here, we must emphasize that the purpose of this thesis at this stage is not to solve this issue. However, further development of the HSO in the future has the potential to facilitate the design of semantic search engines in the domain of human stress.

3.5 Choice of Ontology

Regarding the first research problem, i.e. lack of a formal conceptualization framework in the stress domain, ontology is able to formalize different stress-related concepts and theories in a machine-understandable form, thereby significantly facilitating the process of information retrieval and analysis. The formal structure of ontology also facilitates the process of classification and description of domain concepts and the relationships between them.

3.5.1 Ontology Can Offer a Subject-based Classification System for the Domain

Concerning the first research issue, i.e. lack of an inclusive subject-based classification system for stress-related concepts, ontology allows us to categorize various concepts according to a set of predefined subject categories. For example, using a top-down method of ontology design, experts can initially define several classes of subjects as the higher level categories and link all other concepts in the domain to one or more of those categories according to their role in the domain of interest. In this respect, the HSO's seven sub-ontologies represent different subjects of the human stress domain to which all other stress-related concepts can be connected.

3.5.2 Ontology Can Offer an Overview of Various Research Topics in the Domain

Regarding the second research issue, i.e. difficulty in viewing links between stress-related phenomena, ontology has the potential to provide an overview of various research subjects and empirical findings such that different subjects, concepts, and empirical results can be placed in their proper categories and viewed in relation to one another. Therefore, through the unified and incorporative structure of a given ontology in a domain, some formerly unseen relationships among different aspects of theories and concepts are likely to be revealed, motivating researchers to carry out additional studies to address any gaps or other latent issues across entities and theories. For example, ontology can explicitly explain the potential relations a set of data has with multiplicities of other theories and methods which have addressed relevant aspects of the same phenomenon.

Having an inclusive view of all related phenomena within human stress domain can help us obtain a better understanding of this phenomenon as well as a perspective of gaps and issues observed in its research field.

3.5.3 Ontology Can Facilitate the Process of Data Integration and Interoperation

There are a number of ways ontologies can be used for different data integration purposes. These may include metadata representation, global conceptualization, support for high-level queries, declarative mediation, and mapping support (Cruz & Xiao, 2005).

An example of the use of ontologies for semantic integration and interoperation is as follows: Two XML documents (D1 and D2) have different schemas but contain data with similar meaning (semantics). In D1, the element *Atenolol* is nested under the element *Beta Adrenergic Blocking Agent*, whereas in D2, the element *Tenormin* is nested under the element *βBlocker*. However, the two elements *Atenolol* and *Tenormin* semantically represent the same concept. Similarly, the term *Beta Adrenergic Blocking Agent* is equivalent to the term *βBlocker*. Nevertheless, to reach the two semantically equivalent data elements (e.g. *Tenormin* and *Atenolol*), we have to use two different XML path patterns for each document. Therefore, an XML-based conceptual model requires multiple XML schemas or structures to represent and retrieve a single concept that has several names. In contrast, ontology languages such as RDF and OWL operate on the conceptual level and are structurally flat, enabling the user to formulate his/her query from a conceptual standpoint regardless of the structure of its relevant sources (documents) (Cruz & Xiao, 2005).

The creation of a local ontology from each source database schema can eliminate the heterogeneity of the two abovementioned local sources. Using an XML schema transformation method, we will be able to convert XML complex-type elements into RDF classes. In the same manner, XML simple-type elements and attributes can be converted into RDF properties. The transformation process is also able to encode the mapping information between each RDF ontology concept and its path to its equivalent element in the XML document. In this way, we will be able to retrieve different names or labels for the same ontology concept from different heterogeneous sources (Cruz & Xiao, 2005).

3.5.4 Ontology Can Facilitate the Process of Semantic Search

Ontologies can also be used as a foundation for the design of the *Semantic Web* (Berners-Lee, Hendler, & Lassila, 2001; Maedche & Staab, 2001). The Semantic Web paradigm was proposed as an extension of the current Web with the purpose of organizing and structuralizing the semantic or meaningful content of Web pages. The Semantic Web is equipped with meaningful, organized, explicit, and formally expressed information, allowing automated search engines to reason about the applicant's input queries, map them to the relevant information stored in the Web content, and produce intended, precise, and reliable outputs in accordance with the received input queries (Berners-Lee et al., 2001). The semantic Web utilizes metadata[2], namely data about the data, to describe, encode, organize, classify, and share its data (Handschuh & Staab, 2003).

[2] Metadata provide information on different aspects of data such as the storage facilities they have used, their intended usage, quality, and their content descriptions. A common method used to capture such metadata is Web-page categorization. By use of this method, we assign different Web-pages to specified relevant classes representing different topics or areas of knowledge. Such a classification system is built upon a predefined shared ontology. The Semantic Web search engines, thus, utilize these ontology-based metadata models to access, retrieve, manage, and store topic-relevant Web pages in an intelligent way according to the users' requests (Stuckenschmidt & Harmelen, 2001).

3.6 Choice of the EBEO Methodology

The Evidence-Based Evolving Ontology (EBEO) is an ontology evolution methodology which proposes a solution for the establishment of evidentiary and evolutionary ontology relationships. This methodology uses a counting mode which is adopted from methods of systematic review in order to adjust ontology relationships in proportion with the percentage of evidence obtained from the literature. We developed this methodology as a potential solution to the abovementioned problems in defining ontology relationships across scientific ontologies. Furthermore, the incorporation of Fuzzy Inference System (FIS) in this strategy is in line with previous applications of fuzzy logic in the management of linguistic variables (Nasiri Khoozani, Hussain, Dillon, & Hadzic, 2010).

3.7 Conclusion

Two main research problems were addressed in this thesis. The first problem was lack of a formal conceptualization framework for the description, organization, and classification of stress-related information. To address this problem, we designed a semi-formal conceptualization framework, the HSO, for the description, organization, and classification of stress-related information in human stress domain.

The second problem was lack of an ontology evolution methodology for automatic/evidence-based refinement of ontological relationships. To address this issue, we proposed the EBEO, an ontology with the capability to change its relationships and evolve consistent with the received evidences from scientific literature.

This chapter also elaborated on some of the issues concerning the formal conceptualization of stress knowledge, subject-based organization of stress-related information, interconnection of stress-related concepts, data heterogeneity in the stress domain, retrieval of stress-related information, and need for the establishment of evidence-based ontology relationships within the stress domain. We explained that there is a need for the development of a formal ontology framework in order to facilitate the process of classification and description of stress knowledge. Moreover, we outlined how ontology can help researchers to rapidly access desirable information, search all relevant aspects of one topic in one place, obtain an inclusive view of links and interconnections between dispersed stress-related concepts, and resolve the problem of data heterogeneity within their domain of interest. We also highlighted the importance of having evidence-based and evolving ontology relationships and explained why we developed the EBEO methodology to address this concern. In the next chapter, we present a brief overview of the solution for the abovementioned problems and issues.

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Chapter 4 – Overview of the Solution

4.1 Introduction

To solve the research problems and issues described in the previous chapter, we initially need to build an ontology. The development of the HSO is the proposed solution for the research problem and issues related to the domain of human stress. The other research problem, i.e. lack of an ontology evolution methodology for the automatic/evidence-based refinement of ontological relationships, required a proposal for the establishment of an *Automated Systematic Review Agent* (ASRA) which implements systematic review as a basis for the refinement of ontology relationships. This chapter offers an overview of the stages we undertake to solve the research problems and issues. These stages are as follows:

- Vision Statement and Identification of the Knowledge Resources
- Text Selection and Reuse of other Ontologies
- Conceptualization and Classification of the Domain Knowledge
- Formalization of the Conceptualization
- Evaluation and Refinement of the Ontology
- Development of an Ontology Evolution Methodology for the Evidence-based Evolution of Ontology Relationships

4.2 Vision Statement and Identification of Knowledge Resources

Every ontology-based solution for the conceptualization of a domain initially needs to clarify the aim of the ontology, i.e. "what is the ontology going to be used for?" In line with that, the scope and potential applications of the ontology are to be specified. In this regard, we primarily identify the aim, scope and domain of our ontology. In this first stage, we clearly state the aim of our ontology in terms of its possible applications or cases of use.

Furthermore, we define the range, domain, and limits of our work. For example, we specify the areas of knowledge and science that the ontology aims to represent and the areas that are excluded from our work. Furthermore, we identify the resources and databases from which we extract knowledge for the development of our ontology (Spyns, Tang, & Meersman, 2008). For example, for the domain of human stress we select the Encyclopedia of Stress (Fink, 2007) in addition to other stress-related books and articles. The selected resources must be representative of the domain-related concepts and theories which are used by domain experts and researchers.

4.3 Text Selection and Reuse of other Ontologies

At the second stage, the relevant texts and statements from the specified knowledge resources are selected. Different methods and strategies can be used to extract those sections of the identified knowledge resources which contain relevant concepts and theories for the conceptualization of the ontology. Such relevant sections may also include notions about the definition of concepts and information about the context in which a certain theory holds true (Spyns et al., 2008).

At this stage, we also consider the use of other established ontologies for purposes such as enrichment of our ontology, incorporation of widely-used classification systems, and saving of time and effort (Noy & McGuinness, 2001; Spyns et al., 2008).

4.4 Conceptualization and Classification of the Domain Knowledge

The extracted knowledge from the selected texts is conceptualized and classified at this stage. By ‘conceptualization’ we mean the creation of an abstract model of the domain knowledge. Such an abstract model is defined by the specification of the domain concepts and relationships between them. The resultant model of concepts and their relationships appear in the form of theory statements such as “*X influences Y*”, or “*A is a part of B*”. Concepts are also classified at this stage, creating hierarchies of super-concepts and their related sub-concepts (Noy & McGuinness, 2001; Spyns et al., 2008).

4.5 Formalization of the Conceptualization

To formalize the conceptualization and classification models of the previous stage, we need to implement an ontology language and its corresponding tool. 'Formalization' refers to the translation of the conceptualized knowledge into a machine-understandable and formal language. Ontology tools are usually capable of translating the concept definitions and descriptions into a predefined ontology language in an automatic way. For example, using OWL language, the statement "*X is a subclass of Y*" can be represented in the following form (Dean et al., 2003; Noy & McGuinness, 2001):

```
<owl:Class rdf:about="http://www.example.com/ontologies/example.owl#X">
        <rdfs:subClassOf
rdf:resource="http://www.example.com/ontologies/example.owl#Y"/>
```

4.6 Evaluation and Refinement of the Ontology

In this step, the created ontology is evaluated using a number of criteria such as concept converge, consistency, reusability, clarity, coherence, minimal encoding bias, minimal ontological commitment, simplicity, and correctness (Brank, Grobelnik, & Mladenic, 2005). For the evaluation of our ontology we have used the concept coverage criterion (Hartmann et al., 2005). To estimate the percentage of the domain concepts covered by the developed ontology, we randomly select a set of articles which are published in the domain, extract their professional concepts, and map them to their counterparts in the ontology. In this way, we are able to work out what percentage of concepts within this test set is represented by the ontology. Then, the missing concepts can be added to the ontology to enrich its domain representation.

4.7 Development of an Ontology Evolution Methodology for the Evidence-based Evolution of Ontology Relationships

To find a solution for the defining and refining of ontology relationships based on the evidence obtained from literature, we develop an ontology evolution strategy which can automatically refine ontology relationships in response to the incoming proving or disproving scientific evidence. The implementation of this method entails the incorporation of an automatic agent which employs a reliable mathematical computation for the consistent and evidence-based alteration of ontology relationships. We also need strategies for the constant transfer of theoretical statements within the scientific texts into the automated agent.

4.8 Objectives of Research

The human stress domain contains a huge array of data which are reflected in different databases. In our research, we have established an ontology framework to capture and represent all information related to stress response, its causes, mediators, effects, treatments, measurements, and theories. Furthermore, we proposed a strategy for the evolution of the HSO relationships based on scientific evidence. The objectives of this research are the following:

1. To define the overall purpose, scope, and expected applications of the HSO.

2. To identify and select relevant knowledge resources and materials.

3. To analyse, conceptualise, and classify the knowledge domain of human stress.

4. To transfer the conceptual description into a formal model using an ontology tool.

5. To evaluate the established ontology.

6. To find a solution for the continuous and automatic refinement of ontology relationships based on the evidence obtained from scientific works.

4.9 Conclusion

This chapter outlined the stages undertaken in order to solve the research problems and issues described in the previous chapter. Our solution consists of different stages of ontology building methodology in addition to the proposal of a methodology for the automatic evolution of evidence-based ontology relationships. This thesis follows the objectives of domain and resource identification, ontology conceptualization and classification, ontology formalization, ontology evaluation, and finding a solution for the evidentiality and evolution of ontology relationships. These objectives are described in detail in the following chapters. In the next chapter, we outline our research method.

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Chapter 5 – Research Method

5.1 Introduction

It has been suggested that ontology building is more of a craft than a strict engineering design (Beck & Pinto, 2002), and that we cannot talk about the *correctness* of a certain methodology, since various alternative methodologies can be employed for different applications (Noy & McGuinness, 2001). There are different ontology building methods which can be adopted for solving different data management problems. However, there are more commonalities and overlaps between these methods than there are distinguishable and distinctive differences. This chapter elaborates on the research approach we chose to establish the HSO. It also points to the ontology evolution strategy we proposed for the evidence-based refinement of ontology relationships between concepts.

5.2 The Methodology used for the Development of the HSO

To develop the HSO, we undertook different ontology-building stages which were adopted from a number of ontology-development methodologies such as DOGMA ontology engineering methodology (Spyns, Tang, & Meersman, 2008) and Knowledge Engineering Methodology (Noy & McGuinness, 2001; Uschold & Gruninger, 1996). These steps are as follows:

- Vision Statement and Identification of Stress-Related Knowledge Resources
- Text Selection and Reuse of Other Ontologies in Medical and Health Sciences
- Conceptualization and Classification of Human Stress Knowledge
- Formalization of the Conceptualization

- Evaluation and Refinement of the HSO

Figure 5.1 is a schematic view of different tasks we undertook to develop the HSO.

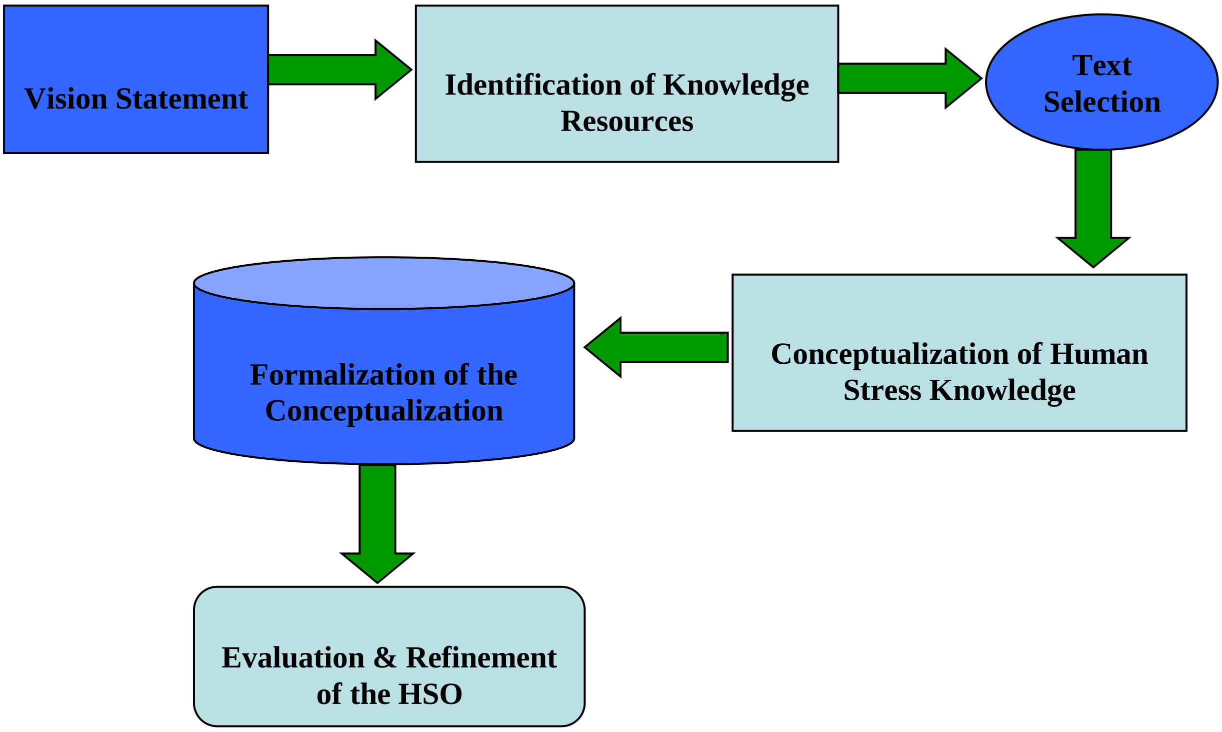

Figure 5.1. A Schematic View of the Ontology Methodology Used for the Development of the HSO

5.2.1 Vision Statement and Identification of Stress-related Knowledge Resources

We initially formulated the vision statement (the overall purpose and potential applications), defined the domain of interest, scope of the project, predicted timeline, and identified the knowledge resources required for the development of the HSO.

The purpose of this thesis was to develop an ontology for the domain of human stress which formally represents knowledge about stress-related concepts and their relationship. This ontology was meant to serve as a conceptual model of stress knowledge with which the following applications would be envisaged:

- Facilitation of information discovery and retrieval
- Data integration

The domain of interest is human stress which is embedded within the fields of psychology, psychiatry, and physiology.

The scope of the project draws on conceptualization of stress knowledge, ontology design, formal representation of the conceptual model by use of the Protégé tool, and evaluation of the HSO.

Although the initial estimated timeline was two years, the project was completed in approximately one year and 10 months.

Our knowledge resources for the human stress domain incorporated the Encyclopedia of Stress (Fink, 2007) in addition to other stress-related psychology and psychiatry texts and electronic resources from various psychology and psychiatry databases such as the PsychInfo database.

5.2.2 Text Selection and Reuse of Other Ontologies in Medical and Health Sciences

We selected relevant passages from the specified knowledge resources in the following method as has been described by Spyns, Tang, and Meersman (2008):

First, we divided each document into "*core text*" and "*explanatory text*". Then we separated out paragraphs with no potential applicability and extracted those sections of the core text which had the potential to form the ontology axioms. After that, by referring to other sections of the text and experts' knowledge, possible exceptions to those axioms were identified. Respectively, definitions for ontology concepts were extracted from relevant texts.

Furthermore, to benefit from the possibility of interaction with other related ontologies, the relevant terms and concepts from MeSH database were selected and incorporated into our conceptual repertory.

5.2.3 Conceptualization and Classification of Human Stress Knowledge

We used a manual strategy to conceptualize human stress knowledge embedded within the selected texts. The conceptualization process began with the identification and recording of all terms and concepts of interest. Initially, we had defined five important concepts as the sub-ontologies under which other concepts could be placed. These major concepts included: 1) *Stress Cause,* 2) *Stress Mediator,* 3) *Stress Effect*, 4) *Stress Treatment*, and 5) *Stress Measurement* (Nasiri Khoozani & Hadzic, 2010). However, later we added two other main concepts, *Stress Response* and *Stress Theory*, to incorporate a range of other stress-related concepts which could not be subsumed by the initially predefined sub-ontologies.

Next, other stress-related concepts were identified and placed under their related categories. Using a Word document, we described and recorded hundreds of concepts, their definitions, binary relationships between them in the form of theoretical axioms, and other contextual information about them. However, this initial concept assignment underwent many alterations as we progressed with our conceptualization task.

This stage was further guided and improved through direct communication with domain experts and use of psychology dictionaries and encyclopedias. Chapter 6 explains the result of our conceptualization in more detail.

5.2.4 Formalization of the Conceptualization

To formalize our conceptualization of stress knowledge, we used the Protégé 4 tool. This tool allows us to store the specified concepts in a class hierarchy and provides facilities for the description and definition of their properties, constraints, and their links with other concepts.

The *class hierarchy* was developed and formalized by means of a combination of top-down and bottom-up classification strategies (Noy & McGuinness, 2001). Using a top-down approach, we initially began with the creation and description of the seven specified general concepts or sub-ontologies. Each of these top-level concepts, then, integrated a number of relevant middle-level concepts. Some of these middle-level concepts were defined via a top-down method. Others were formed using a bottom-up approach through which we first identified several specific concepts (e.g. concepts relevant to the length of stressors) and then abstracted a more general and representative concept for them (e.g. *Stressor Duration*). In the next stage, we specified the properties (relationships) of the concepts and classified them in the *object property hierarchy* view.

The classified concepts of the *class hierarchy* were then defined and described using the object properties. Object properties represent ontological relationships which link different classes (concepts) together.

Furthermore, we were able to add comment, label, definition, and other metadata to our concepts and axioms and restrict their application to certain contexts.

The Protégé tool automatically translates concept definitions and descriptions into the formal OWL language which appears in the following form:

```
<owl:Class rdf:about="http://www.hso.com/ontologies/hso.owl#AcutePain">
        <rdfs:subClassOf
rdf:resource="http://www.hso.com/ontologies/hso.owl#Pain"/>
        <rdfs:subClassOf>
            <owl:Restriction>
                <owl:onProperty
rdf:resource="http://www.hso.com/ontologies/hso.owl#canIncrease"/>
                <owl:someValuesFrom
rdf:resource="http://www.hso.com/ontologies/hso.owl#Catecholamine"/>
```

```
        </owl:Restriction>
    </rdfs:subClassOf>
</owl:Class>
```

Further details about the ontology language and tool functions are presented in Chapter 7.

5.2.5 Evaluation and Refinement of the HSO

The established ontology was finally evaluated through the evaluation of its conceptual coverage. By use of a randomly selected test set we evaluated whether the ontology represents the majority of stress-related concepts used in the literature. The stress-related concepts abstracted from this test set were given to the ontology tool. Then we calculated the percentage of concepts within this test set that had equal or similar concepts in the HSO. In the later stages of the ontology evolution, new concepts will be added and created axioms will be further refined to ensure the ontology meet the reusability, consistency, clarity, coherence, minimal encoding bias, minimal ontological commitment, simplicity, and correctness criteria. The process of conceptual coverage method and our evaluation results are explained in Chapter 9.

5.3 Development of a the EBEO Methodology for the Evolution of Ontology Relationships

We proposed an ontology evolution strategy in order to address an important relationship issue in a scientific ontology: the evidentiality of existing relationships between represented concepts in an ontology. To address this issue, our methodology integrates a higher-level ontology, i.e. Systematic Review Ontology (SRO), into a Systematic Review Agent (ASRA) which employs a Fuzzy Inference System (FIS) in order to automatically modify ontological relations in a domain ontology based on the evidence received from information resources. Details of this approach are presented in Chapter 8.

5.4 Conclusion

We described the ontology-building method employed for the design of the HSO. To develop the HSO, we undertook different stages of vision statement and identification of knowledge resources, text selection, conceptualization and classification of human stress knowledge, formalization of the conceptualization, and evaluation and refinement of the HSO. However, further strategies are needed for the refinement and evolution of the HSO. In the next chapter, we present a review of the conceptualized and classified knowledge of human stress.

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Chapter 6 – Conceptualization and Classification of Human Stress Knowledge

6.1 Introduction

The HSO is an integrative and computer-readable knowledge model of existing concepts and their relationships within the domain of human stress. This chapter describes this knowledge model and explains some of the higher-level concepts and theories which have been represented in our ontology of human stress. The chapter can also be considered as a review of various aspects of human stress which are being studied by experts and researchers across domains of psychology, psychiatry, and medicine. We have also included figures from the Protégé tool to visually represent our concept hierarchies.

6.2 HSO Structure

The structure of this ontology is made up of seven sub-ontologies as follows:

1. Stress Cause
2. Stress Mediator
3. Stress Response
4. Stress Effect
5. Stress Treatment
6. Stress Measurement
7. Stress Theory

Stress-related concepts and entities fall under their corresponding categories which are incorporated into each of these sub-ontologies. Nevertheless, concepts are not mutually exclusive; i.e. it is possible that one concept appears under more than one category and sub-ontology. This notion is particularly in compliance with the nature and role of many concepts in the field of stress as often they take multiple roles and can be categorized differently depending on the context in which they are used. For example, *Erectile Dysfunction* can be simultaneously categorized under sub-ontologies of *Stress Effect* and *Stress Cause* as it is as much an effect of stress as it is a cause of it. This concept, therefore, has been classified under the categories of *Psychiatric Disorder* and *Psychological Stressor* which belong to the sub-ontologies of Stress Effect and Stress Cause correspondingly.

The HSO is also linked to some of the concepts and vocabularies of MeSH (National-Library-of-Medicine, 2010). There were a number of concepts relevant to the domain of stress which could not be directly placed under any of the specified sub-ontologies of the HSO. For example, the concept *Oxytocin* which is a type of *peptide*, has some associations with stress reaction (e.g. can be increased by stress reaction). However, it could not be slotted directly into any of the HSO sub-ontologies. Therefore, we had to adopt a number of categories and their related concepts from MeSH in order to enrich our ontology. These categories are placed under a separate ontology labelled *MeSH Category* rooting from `Thing`. The MeSH Category ontology included five categories of MeSH which contained vocabularies related to the knowledge of human stress (Figure 6.1). These categories are as follows:

1. Anatomy Category
2. Chemicals and Drugs Category
3. Disease Category
4. Phenomena and Processes Category
5. Psychiatry and Psychology Category

In this way, we were able to place the abovementioned concept *Oxytocin* under the class of *Peptide* which falls under the Chemicals and Drugs Category of MeSH.

The following gives a brief description of each sub-ontology of the HSO together with a succinct account of a number of corresponding concepts and relationships appearing in the literature on human stress.

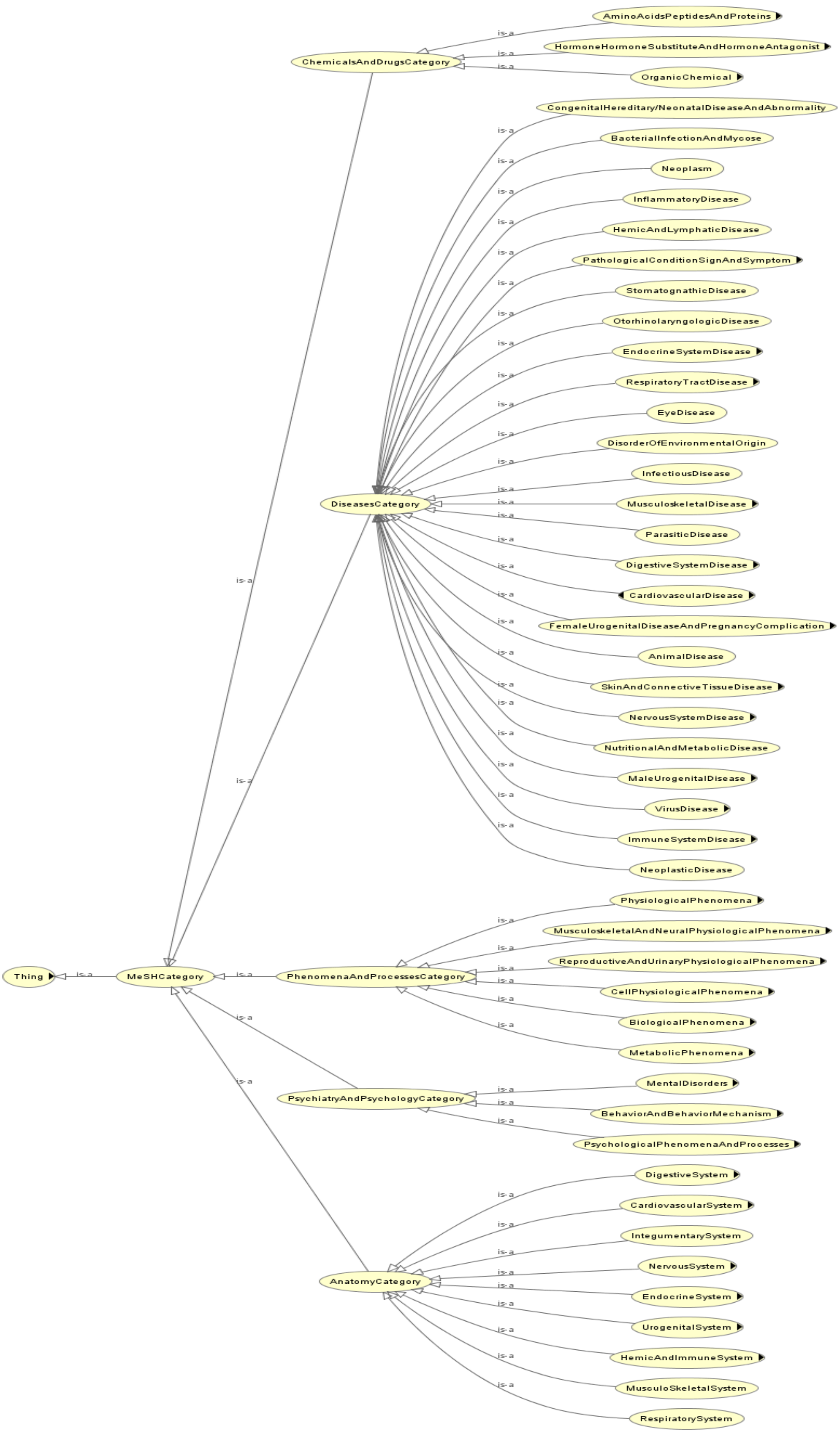

Figure 6.1. MeSH Category

6.3 Stress Cause (Stressor)

The sub-ontology of *stress cause* or *stressor* incorporates five general classes of stress-generating factors with respect to their *relativity*, *objectivity*, *duration*, *proximity*, and *severity*. These are as follows:

- Stressor Relativity
- Stressor Objectivity
- Stressor Duration
- Stressor Proximity
- Stressor Severity

6.3.1 Stressor Relativity

According to one classification system (Girdano, Dusek, & Everly, 2001; Lupien, Maheu, Tu, Fiocco, & Schramek, 2007) stressors, with respect to their relativity, are grouped into two classes:

- Relative (Psychological) Stressor
- Absolute (Biogenic) Stressor

6.3.1.1 Relative (Psychological) Stressor

The degree of stressfulness of relative or psychological stressors depends on our appraisal and interpretation of events. This means that the individual must perceive an encountered incident as threatening or challenging in order for that incident to be considered a stressful event (Lazarus & Folkman, 1984). An example of this stressfulness relativity is the stress, for different students, of failing a final exam. Although there exists one stimulus (i.e. the final exam) for all students in a given situation, the stressfulness of that stimulus differs from individual to individual depending on their different psychological backgrounds.

Furthermore, it has been shown that even though some stimuli are essentially menacing to all individuals, people still tend to respond and cope differently depending on their particular systems of appraisal and interpretation (Folkman & Lazarus, 1980).

This account of stressor relativity was particularly highlighted in Lazarus's *theory of appraisal* (Lazarus, 1966). Accordingly, psychological stress is neither merely in the environment nor caused solely by individual psychological attributes, but is a product of the person-environment relationship (Lazarus, 2006). The HSO presents *relative stressor*s under categories such as:

- Psychological Stressor
    - Developmental Stressors
        - Infancy (e.g. Maternal Separation)
        - Childhood (e.g. Parental Punishment)
        - Adolescence (e.g. Identity Stressor)
        - Adulthood (e.g. Job Stressor)
        - Elderly (e.g. Aging))
    - Emotional Stressor (e.g. Fear, Anger, Anxiety, Guilt, etc)
    - Sexual Stressor (e.g. Sexual Identity Confusion, Sexual Victimization)
- Social Stressor
    - Family Stressor (e.g. Marital Separation)
    - Work-Related Stressor (e.g. Unemployment)
    - Immigration Stressor (e.g. Acculturation)
    - Natural Disaster Stressor (e.g. Flood)
    - etc

6.3.1.2 Absolute (Biogenic) Stressor

Biogenic or *absolute stressor*s, in contrast, influence the organism regardless of the individual's appraisal and perceptions of them. Stimuli with sympathetic effects, such as cocaine and amphetamines or extreme temperatures that result in physiological arousal, are categorized as biogenic or absolute stressors (Lupien et al., 2007). We have identified three general categories of absolute stressors:

- Chemical Stressor (e.g. Ether, Poison)
- Physical Stressor (e.g. Vibration, Noise, Heat)
- Physiological Stressor (e.g. Excessive Exercise, Haemorrhage, Hyperventilation)

6.3.2 Stressor Objectivity

According to another classification system (Pervin, 1978), stressful stimuli can be classified into two clusters:

- Objective Stressor
- Subjective Stressor

6.3.2.1 Objective Stressor

An objective account of stress-inducing situations has to do with the objective definitions of harmful and stress-producing dimensions of such situations. By using objective specifications of stressors, compared to subjective determinants of feelings of stress, psychologists can gain a better understanding and assessment of the nature and mechanisms of cognitive deviation and misinterpretation processes in individuals suffering from experiences of excessive stress (Vollrath, 2001). Furthermore, objective measures of stressful events allow researchers to evaluate the existence of possible correlations between the incidence of certain *identifiable* events and their corresponding augmented risk for development of disease. Objective evaluations, moreover, can reduce the probability of individuals giving biased and subjective accounts of the past events (Cohen, Kamarck, & Mermelstein, 1983a). Objective stressors are amalgamated under two classes:

- Absolute Stressor

- Stressful Life Event

6.3.2.2 Subjective Stressor

A subjective account of stressful situations is determined by different personality traits including various dominant motives, needs, desires, and coping strategies (Funder & Colvin, 1991). For example, to categorize the trait of *risk-seeking behaviour* as a stressful stimulus, we need to take into account those particular personality characteristics that contribute to the aggravation of such behaviours (Vollrath, 2001). In addition, it has been emphasized that the expression of such personality traits may differ depending on different *situations* to which an individual encounter (Ten Berge & De Raad, 1999). Subjective stressors can be placed under the classes of relative stressors:

- Relative Stressor
    - Psychological Stressor
    - Social Stressor

6.3.3 Stressor Duration

Stressors, in a widely-used classification system within psychology and psychiatry domains are categorized according to their duration into:

- Acute Stressor
- Chronic Stressor

6.3.3.1 Acute Stressor

*Acute stressor*s are brief and transient, while *chronic stressor*s are by nature persistent and lasting. Nevertheless, acute stressors can result in enduring feelings of stress and its subsequent physiological alterations. An example of this phenomenon is the enduring symptoms observed in *Post Traumatic Stress Disorder* (PTSD) after the occurrence of an acute trauma (Baum, O'Keeffe, & Davidson, 1990). Acute stressors come under categories such as:

- Acute Trauma (e.g. Crisis, Accident)
- Early Adverse Experience (e.g. Child Abuse, Adverse Medical Procedure)
- Acute Physiological Stressor (e.g. Acute Pain, Hypoxia)
- Acute Physical Stressor (e.g. Immobilization, Exposure to Repeated Stimulus)

6.3.3.2 Chronic Stressor

Chronic stressors, in contrast, are less severe but of a more ambiguous and enduring nature (Baum et al., 1990). They tap into detrimental, threatening, and continuous situations which run in one's life such as the demanding stressful roles he/she has to take at work or family contexts (Lazarus, 2006). Some types of chronic stressors include:

- Chronic Social Stress (e.g. Crowding, Poverty)
- Chronic Strain (e.g. Role Burden)
- Interpersonal Conflict (e.g. Family Stressor, Relationship Difficulty)
- Medical Condition (e.g. Medical Disability, Chronic Illness)
- Hassle (e.g. Misplacing Things)
- Continuing Adverse Condition (e.g. Living with Handicap) (Kanner, Coyne, Schaefer, & Lazarus, 1981)

6.3.4 Stressor Proximity

Studies that have considered the *time range* in their conceptualization and evaluation of stress have often classified stressors into:

- Distal Stressors, and

- Proximal Stressors (Ensel & Lin, 1996)

6.3.4.1 Proximal Stressor

*Proximal stressor*s include those acute stressful stimuli that have recently (e.g. within the past year) been experienced by the individual (Ensel & Lin, 1996). Such stressors can appear under the wide-ranging class of:

- Proximal Acute Stressor

6.3.4.2 Distal Stressor

*Distal stressor*s, in contrast, imply the remote stressors that were experienced in the distant past e.g. in early childhood or adolescence (Ensel & Lin, 1996). Researchers in the field of stress have shown that distal stressors such as early childhood life events can moderate the effect of recent proximal stressors on individuals (Brown & Harris, 1978; Hammen, 2005). For example, studies have demonstrated that distal stressors can significantly predict and affect the development and recurrence of current levels of depression (Ensel & Lin, 1996; Hammen, 2005). Distal stressors such as childhood abuse can also alter an individual's immune system, making him/her vulnerable to a variety of diseases (Segerstrom & Miller, 2004). Distal stressors are categorized under the general class of:

- Early Adverse Experience
  - Adverse Medical Procedure
  - Child Abuse
  - Maternal Separation
  - etc

6.3.5 Stressor Severity

With regard to the severity and impact of an event on the individual, stressors can be classified as:

- Major Stressor, or
- Minor Stressor (Pillow, Zautra, & Sandler, 1996)

6.3.5.1 Major Stressor

*Major stressor*s or *major life events* can be defined as those severe life incidents (e.g. divorce) as a result of which an affected individual needs a major life readjustment (Holmes & Rahe, 1967; Pillow et al., 1996). Major stressful life events can cause negative emotions and elicit physical reactions (Fink, 2007). In the context of stress-related disorders, a stressful life event is a severe challenging incident that potentially contributes to the onset, incidence, or deterioration of a psychopathological symptom or disorder (Phillips, Francey, Edwards, & McMurray, 2007). Major stressors often precede episodes of major depression (Hammen, 2005) and schizophrenia symptoms of deterioration and relapse (Phillips et al., 2007). The following categories incorporate a wide range of major stressors:

- Acute Trauma
- Traumatic Family Event
- Early Adverse Experience

6.3.5.2 Minor Stressor

*Minor stressor*s or *daily hassles* are minor and small events (e.g. daily work concerns or argument with children) which occur on a daily basis in the individual's life (Serido, Almeida, & Wethington, 2004). Overall, daily hassles and their consequent emotional effects are supposed to fade away within two days (Bolger, DeLongis, Kessler, & Wethington, 1989). However, it has been reported that the type and frequency of encountered minor stressors or daily hassles can predict some corresponding somatic and mental health outcomes more so than do the recent major stressors (Bolger, DeLongis, Kessler, & Wethington, 1989; Kanner et al., 1981; Lazarus, 1984b). For example, minor daily hassles can precipitate psychotic symptoms in vulnerable individuals (Phillips et al., 2007). Minor stressors may include:

- Work Concern
- Daily Arguments
- Brief Naturalistic Stressor (e.g. Public Speaking)

Figure 6.2 is the graphical representation of *stress cause* sub-ontology as drawn by the Protégé tool.

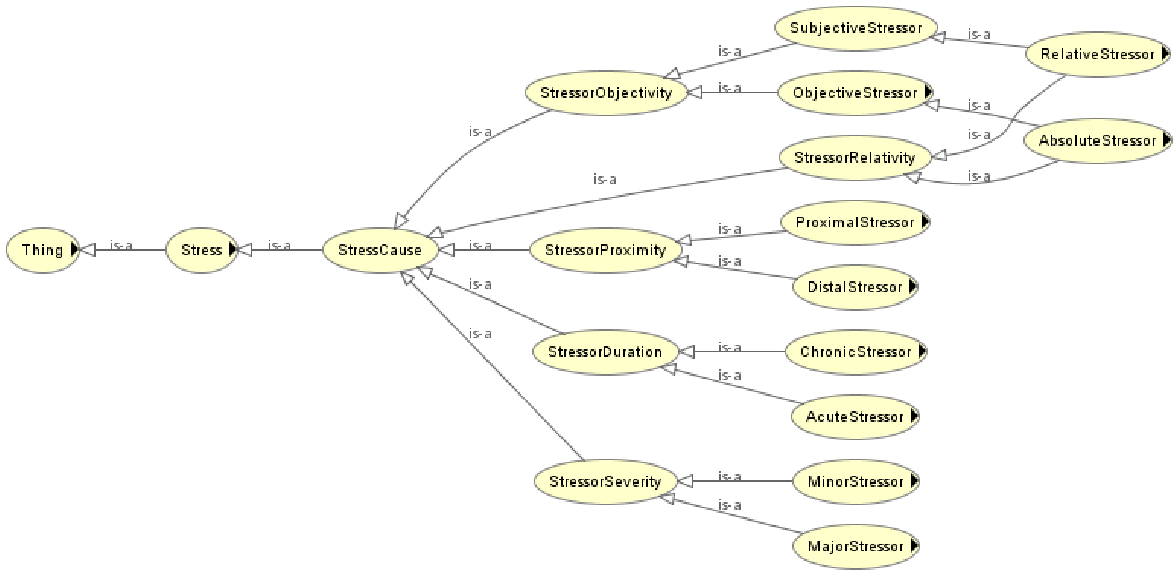

Figure 6.2. Stress Cause Sub-ontology

6.4 Stress Mediator

The path from exposure to a stressor to the experience of stress is not a direct path, but indeed, an amalgamation of biological, psychological, and situational mediators mediate the course from stress causes to stress response, and their resultant stress effects. The HSO has classified stress mediators into three general categories (Nasiri Khoozani & Hadzic, 2010):

- Biological Mediator
- Psychological Mediator
- Situational Mediator

Each category incorporates a number of concepts as follows:

6.4.1 Biological Mediator

Biological mediators include a wide range of:

- Neurophysiological Mediator
- Physiological Mediator
- Biological Risk Factor

6.4.1.1 Neurophysiological Mediator

The HSO *neurophysiological mediator*s include the following categories:

- Primary Stress Effector System
- Nervous System Physiological Process
- Stress Hormone
- Stress Hormone Receptor
- Stress Protein
- Chronobiology Phenomena

6.4.1.1.1 Primary Stress Effector System

*Primary Stress Effector System*s activate physiological as well as behavioural responses in the face of acute stressors (Pacak & McCarty, 2007). Activation of the *Hypothalamic Pituitary Adrenocortical* (HPA) axis and its consequent hormone secretion allows the organism to express its adaptive fight-or-flight response when facing a stressful agent. However, if the

HPA axis remains over-active for a long time, the organism will undergo some consequent harmful alterations such as infection induced by the suppression of the immune system (Avila, Morgan, & Bayer, 2003), augmented blood pressure, hypertension, arterial conditions, or diabetes (See (McEwen, 2000) for a general review). The primary stress effector systems include:

- Sympathetic Nervous System
- Parasympathetic Nervous System
- Adrenomedullary System
- Hypothalamic Pituitary Adrenocortical System
- Rennin Angiotensin System (Pacak & McCarty, 2007)

6.4.1.1.2 Nervous System Physiological Process

Stress response is influenced and mediated by physiological processes which occur in the nervous system. Physiological processes tap into neurological tendencies and alterations in different parts of nervous system. One such neurological tendency is *neurochemical signature* (Pacak et al., 1998).

Selye emphasized that stress is "*the non-specific response of the body to any demand*" (Selye, 1950b, 1976a) (P.53), ruling out the inclusion of specific physiological changes, which might be induced by certain stimuli, in the conceptualization of stress concept (Selye, 1985). However, later researchers reported different specificities of stress response to various stress-inducing agents. For example, Gaillet et al. (1991) demonstrated that the participation of noradrenergic ascending pathways in the stress-induced activation of HPA differs when different types of stressors are involved. This has resulted in some researchers proposing an alternative view, the "*primitive specificity of stress responses*" (Goldstein, 1995), to the theory of stress non-specificity. According to this view, each stressor generates a distinct neurochemical signature which engages, qualitatively or quantitatively, different central and peripheral physiological mechanisms. Such neurochemical alterations are not isolated from, but congruent and cooperative with, other corresponding physiological and behavioural alterations (Pacak et al., 1998).

The physiological processes of the nervous system also include transient and long-lasting alterations which may occur as a result of encounter with acute trauma or chronic excitatory stressors. For example, acute and chronic stressors can bring about the *kindling effect* resulting in *limbic hypersensitivity* (Goddard & Douglas, 1975). If limbic structures are exposed to repeated stimuli, they may become inclined to spontaneous excitation and decrease their convulsive threshold. Activating effects of this phenomenon on different neuroendocrine, endocrine, and arousal systems might explain many stress-related psychological or physiological disorders (Everly, 1985).

Other mediating physiological processes of the nervous system incorporate vital processes such as *sleep*. It has been shown that sleep modifies the level of cortisol secretion and diurnal patterns (Turner-Cobb, 2005). For example, sleep can lower the level of cortisol (Kanaley, Weltman, Pieper, Weltman, & Hartman, 2001).

The physiological processes of the nervous system include:

- Neurochemical Signature
- Kindling Effect (e.g. Limbic Hypersensitivity)
- Sleep
- Stress System Plasticity

6.4.1.1.3 Stress Hormone

Stress hormones consist of *Corticosteroids* (*Glucocorticoids* and *Mineralocorticoids*), and *Catecholamines* (*Adrenaline* and *Noradrenaline*) (McEwen, 1998).

Stress-induced released steroids (Glucocorticoids) are able to pass the blood-brain barrier and affect memory and learning functions in corresponding brain regions including the hippocampus, amygdala, and frontal lobes. Adrenaline, through its effects on the sensory vagus outside the blood-brain barrier and the transition of its data via the nucleus of the solitary tracts, can stimulate the adrenergic receptors of the amygdala. Amygdala is responsible for the process of fear response and storage of emotion-related information (See (Lupien et al., 2006) for review).

One type of Mineralocorticoid hormones is a steroid hormone called *Aldosterone* which is generated by the outer-section (*Zona Glomerulosa*) of the adrenal cortex located in the adrenal gland. By enhancing reabsorption of sodium and water and release of potassium in the kidneys, Aldosterone can augment blood pressure and tension (Williams & Williams, 2003). As Glucocorticoids, Catecholamines, and Aldosterone are stimulated by *Adrenocorticotropic Hormone* (ACTH), their secretion can be escalated by stress response (Gunnar & Quevedo, 2007; Walton, Pugh, Gelderloos, & Macrae, 1995; Williams & Williams, 2003).

Stress hormones are categorized as:

- Stress Hormone Type
    - Corticosteroid
        - Glucocorticoid (Cortisol, Cortisone, Corticosterone)
        - Mineralocorticoid (Aldosterone, Deoxycorticosterone)
    - Catecholamine
        - Adrenaline
        - Noradrenalin
- Stress Hormone Secretion
    - Stress Hormone Dysregulation
        - Physiological Positive Feedback Cycle

<u>6.4.1.1.4 Stress Hormone Receptor</u>

By observing the different effects of stress hormones on the brain, scientists speculated on the existence of different types of receptors which ostensibly are responsible for various and sometimes contrary Glucocorticoid-induced cognitive or memory changes (De Kloet, Joëls, & Holsboer, 2005).

It has been proposed that it is the differences in the affinity of the Type I (*Mineralocorticoid*) and Type II (*Glucocorticoid*) receptors which result in the reported stress hormone-induced differences across various times and within different situations (Reul & De Kloet, 1985). Reportedly, whether Glucocorticoids influence cognitive or memory processes in a positive or negative way depends highly on the ratio of Glucocorticoids occupying each of these receptors (De Kloet et al., 2005).

For example, some studies postulate that when the Type I/Type II ratio is high (when a greater number of Type I receptors are occupied by Glucocorticoids than are Type II receptors), the individual's cognitive functioning augments (Diamond, Bennett, Fleshner, & Rose, 1992). Contrarily, a low Type I/Type II ratio may bring about cognitive deficits (De Kloet, Oitzl, & Joels, 1999). Other studies show that a reduction in the volume of Glucocorticoid receptors in hippocampus areas can be associated with *bipolar disorders* and schizophrenia (Walker, Mittal, & Tessner, 2008).

Stress hormone receptors include Glucocorticoid receptors with their corresponding concepts as follows:

- Glucocorticoid Receptor
  - Glucocorticoid Receptor Type
    - Type I Glucocorticoid Receptor (Mineralocorticoid)
    - Type II Glucocorticoid Receptor (Glucocorticoid)
  - Glucocorticoid Receptor Ratio
    - Type I/Type II Ratio
  - Glucocorticoid Receptor Density
    - Glucocorticoid Receptor Reduction

6.4.1.1.5 Stress Protein

Stress proteins (also called *heat shock proteins*) are a group of ubiquitous proteins which are generated by cells in response to various environmental or physiological stressors in order to increase their tolerance to the effects of the experienced stress and protect their function

(Morimoto, TissieÁres, & Georgopoulos, 1994). It has been shown that stress proteins such as *Annexin* can mediate stress-produced transcriptional activation of the cells as well as contribute to some pathological conditions such as *autoimmune disease* (Rhee, Kim, Huh, & Kim, 2000). Stress proteins may include:

- Chaperone Protein
- Annexin
- etc

6.4.1.1.6 Chronobiology Phenomena

Chronobiology phenomena (*biological rhythms*) are those cyclic, periodic, or time-related phenomena such as *circadian rhythm* which determine some of the physiological patterns such as sleeping and feeding in the organisms (Dunlap, Loros, & DeCoursey, 2004). Various studies have shown that there is a cyclic (with a period of 24 hours) calendar for the secretion of adrenal steroids in organisms (Muller, Manning, & Riondel, 1958). This may cause chronic stress to affect the adrenal function in patients with psychiatric conditions in a selective manner during different circadian phases (Curtis, Fogel, McEvoy, & Zarate, 1966). Furthermore, some studies suggest that major depressive disorders are associated with the disturbed temporal pattern of cortisol such as flattened circadian curve and higher evening cortisol level (Keller et al., 2006). Chronobiology phenomena incorporate:

- Periodicity (e.g. Circadian Rhythm)

6.4.1.2 Physiological Mediator

Physiological mediators relate to *physiological processe*s such as *homeostasis* and *allostasis*, and *nutritional states* of an organism which mediate its stress response. Homeostasis implies the coordinated physiological processes which maintain the internal state of an organism balanced and stable (National-Library-of-Medicine, 2010). Failure of the organism to regain its state of homeostasis, after its disturbance by stressors, may result in adaptation diseases and even death (Selye, 1976b). The mediating role of homeostasis in production of stress response and effects is particularly highlighted by those researchers (e.g. Chrousos & Gold, 1992) who define stress as a state of threatened and disturbed homeostasis.

Allostasis, in a broader sense, is a type of physiological adaptation which helps the organism to regain equilibrium by switching on and switching off its allostatic systems such as *autoimmune nervous system*, *neuroendocrine system*, and *immune system*. Allostasis allows the organism to increase and reduce required hormones such as Noradrenalin in response to threatening or relaxing situations correspondingly (National-Library-of-Medicine, 2010).

The nutritional states of the organism constitute several other physiological mediating factors which exert influence on the stress response. For example, *nutritional intake* can escalate levels of cortisol (Walker et al., 2008).

Physiological mediators can be classified as the following:

- Physiological Process
    - Homeostasis
    - Allostasis
    - Physiological Conditioning
- Nutritional State
    - Nutritional Intake

6.4.1.3 Biological Risk Factor

Another significant cluster of biological mediators taps into the *biological risk factor*s which include various dimensions of *genetic mediators*. Developmental researchers investigating the effects of adverse childhood experiences on stress and emotion reactivity have addressed the significance of individual differences and their corresponding genetic background as possible mediators of such effects (Gunnar & Quevedo, 2007). For example, a large number of studies have investigated the role of *genetic disposition*s and *behavioural temperament*, particularly in cases of *extreme shyness* or *behavioural inhibition*, in the augmented risk of depressive and anxiety disorders (Kagan, Reznick, & Snidman, 1987). Some research works have suggested that the presence of a common regulatory variant (5-HTTLPR) located in the serotonin transporter gene (SLC6A4) may be responsible for the observed escalated risk for depressive and anxiety disorders (Lesch, 2001). Nevertheless, other studies emphasize that such genetic factors can express their effects only when the individual has experienced stressful events such as child maltreatment or lack of social support during his/her childhood (Kaufman et al., 2004). Hence, maternal care can moderate people's gene-regulated patterns of stress reactivity (e.g. adrenal release) and stress resilience (Caldji et al., 1998; Gunnar & Quevedo, 2007; Hane & Fox, 2006).

The HSO has placed the biological risk factors under the following class and subclasses:

- Genetic Mediator
    - Genetic Disposition
    - Heredity
    - Gene Expression
    - Family History of Psychopathology
    - Genetic Polymorphism
    - etc

Figure 6.3 provides a graphical illustration of the HSO biological mediators.

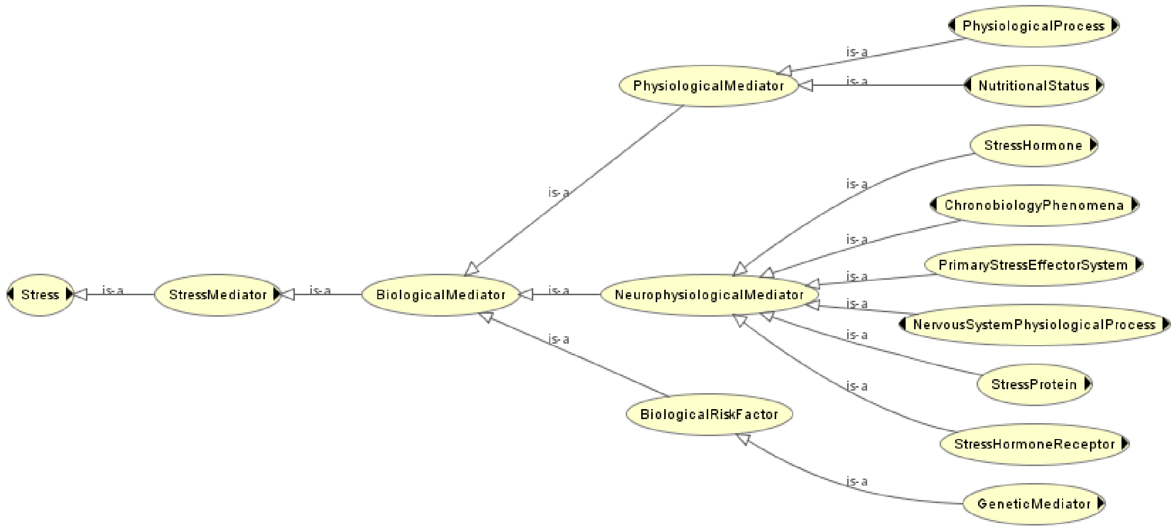

Figure 6.3. Biological Mediator

6.4.2 Psychological Mediator

The spectrum of *psychological mediators* covers a wide range of psychological studies from the realm of emotion and cognition to the challenging phenomena of coping and personality patterns. Psychological mediators appear under the nine general categories of:

- Cognitive Mediator
- Emotional Mediator
- Coping Mediator
- Personality Mediator
- Developmental Mediator
- Personal Resource
- Individual Life Experience
- Gender Related Mediator
- Relationship Mediator

6.4.2.1 Cognitive Mediator

The systematic examination of the mediating role of *cognitive appraisal* and interpretation in association between stress exposure and the consequent emotions was initiated by Arnold (1960) (Everly & Lating, 2002). Later the importance of cognitive processing in human's stress response was underlined by cognitive theories of stress particularly the *transactional theory* of Lazarus and Folkman (1984). The transactional theory suggests that the stressfulness of an experienced event is largely determined by the individual's *cognitive appraisal* and his/her *transaction* with the environment (Lazarus & Folkman, 1984).

The concept of appraisal has a richer meaning than *perception*. It can be defined as a set of cognitive actions through which an individual, consciously or unconsciously, deliberately or non-deliberately (Lazarus, 1982), evaluates the personal significance of an event (Lazarus, 2006).

There are two stages of appraisal. In the first stage, *primary appraisal*, the individual perceives whether an encountered stimulus or event is menacing or harmless. Then, at the second stage, *secondary appraisal*, s/he evaluates her/his abilities and capabilities to manage, resolve, remove, or avoid that potential source of stress (Lazarus & Folkman, 1984).

Lazarus (1966) distinguishes three types of psychological stress, i.e. *harm/loss*, *threat*, and *challenge*, which are based on different appraisals. Harm/loss imply a harm or loss which has already occurred, whereas threat indicates harm or loss which is likely to occur. On the other hand, challenge refers to the individual's feeling that s/he is able to conquer hardships on her/his way to reach the goal through vigour, perseverance, and self-confidence. People tend to cope with each type of these stresses in a different way. Moreover, the psycho-physiological and functional consequences of each stress type turn out to be different (Lazarus, 2006).

Lazarus' explanation of appraisal primacy has been acknowledged by many researchers (Everly & Lating, 2002). However, some scientists (e.g. Zajonc, 1984) argued that an emotional reaction may occur without being preceded by any underlying cognitive construct. Other researchers have highlighted the significance of further cognitive mediators such as *perceived support* (Dunkel-Schetter & Bennett, 1990) in buffering the individual against the detrimental effects of excessive stress in threatening situations.

Another aspect of cognitive mediation in stress-related phenomena relates to the role of cognitive factors in the development and maintenance of mental disorders. For example, research on the mediating dysfunctional cognitive factors contributing to the development of PTSD suggests that vulnerable individuals hold two central *dysfunctional beliefs*: (1) *the world is so perilous*, and (2) *I am not competent enough to deal with it* (Foa & Rothbaum, 1998). Other related cognitive factors incorporate different *habits of thought* such as *autonomy* or *sociotropy* (Beck, 1983) which increase the susceptibility of individuals to different anxiety and depressive disorders (Robins, Bagby, Rector, Lynch, & Kennedy, 1997).

A further important cognitive mediator in stress response is *perceived control*. The concept of control can be defined as the individual's perceived ability to change or handle an environmental transaction (Bandura, 1997). Control may take various behavioural, informational, decisional or cognitive forms. Cognitive control is regarded as the most pertinent control to the human stress response (Sarafino, 1998). In this regard, Albert Bandura (1997) held that the intensity and chronicity of human stress is managed mostly by perceived control over life's demands.

Other control-related factors such as *novelty*, *unpredictability*, *uncontrollability beliefs* (Mason, 1968) and *threat perceptions* (Dickerson & Kemeny, 2002) have also been demonstrated to mediate a person's stress response in a given situation (Lupien et al., 2007). Moreover, evidence indicates that augmentation of patients' perceived control may facilitate their process of recovery and rehabilitation (Johnston, Gilbert, Partridge, & Collins, 1992). The concept of control is a critical axis for nearly all psychotherapy strategies such that treatment can greatly rely on assisting the patient to re-gain control of his/her emotions and the encountered situations (Strupp, 1970).

Some of the classified cognitive mediators of the HSO include:

- Cognitive Appraisal
- Belief (e.g. Dysfunctional Belief)
- Attitude
- Habit of Thought (e.g. Autonomy, Self-Criticism, Sociotropy, etc)
- Perceived Control
- Predictability
- Novelty
- Familiarity
- Ambiguity
- Perceived Support
- Stress Consciousness
- Threat Perception
- Information Retrieval
- etc

6.4.2.2 Emotional Mediator

One of the earliest objections to Selye's theory of stress non-specificity was Mason's (1968) argument that *specific* psychological factors such as *emotions* play a significant role in generating *selective* stress response. He suggested that the exhibition of similar neuroendocrine reactions to different sources of stress is based on the individual's elicitation of emotions such as fear or anxiety (Mason, 1975).

There have also been discussions on whether emotional response to stressors has to be mediated by cognitive appraisal or can happen in isolation from cognitive processes. Overall, there are two opposing views in this regard.

On one side, there are theories and studies supporting the independence of affect and cognition and even the primacy of emotional response over cognitive perception (e.g. Zajonc, 1984). Adherents of this perspective refer to experimental studies showing the automatic emotional responses of the organism to certain stimuli (Steiner, 1974). Accordingly, the organism is basically pre-programmed to react in a particular way (e.g. approach or avoidance) when facing certain types of stimuli. This selection of reaction is due to the existence of some features (such as the extent of neural firing) of afferent excitation. This afferent excitation primarily obtains its affective potential via cognitive processes; however, it may later become autonomous and capable of reacting without the mediation of cognitive processes (Zajonc & Markus, 1982). Zajonc (1984) points to the adaptive value of autonomous emotional reactions and holds that the classification of the environmental stimuli into *dangerous* and *harmless* categories is conducted by our emotional reactions rather than by cognitive appraisal. In support of Zajonc's view, several recent studies on the role of amygdala in the emotion processing show that amygdala can receive signals about the emotionally important stimuli, even when they are subliminally presented, rapidly and earlier than individual's conscious awareness of those stimuli (Phelps, 2006; Whalen et al., 1998). Studies on *fear conditioning* also demonstrate that the emotional properties of a stimulus (stressor) can be generalized to a neutral stimulus, resulting in the organism's conditional fear response (Maren, 2001).

On the other side, the theory of cognitive primacy (Lazarus, 1984a, 2006) holds that every emotion is necessarily preceded and induced by some form of cognitive function and processing about the world or others. Lazarus refutes the reported evidences on the independence or primacy of emotion, for example, by not recognizing states such *arousal* as emotion (Lazarus, 1984a). Recent studies in the field of cognitive neuroscience point to the intertwinement and complexity of emotion and cognition to the extent that setting a clear-cut division between them does not seem promising and practical (Phelps, 2006).

Other lines of study highlight the importance of emotion regulation in stress management strategies (Gross, 1999), as well as the consequences of emotional deprivation for physical and mental health (Charmandari, Tsigos, & Chrousos, 2005).

Emotional mediators include:

- Emotional Processing
- Emotion Regulation
- Emotional Deprivation

6.4.2.3 Coping Mediator

Coping can be defined as the individual’s efforts to diminish or avoid the undesirable psychological or behavioural consequences of stress (Everly & Lating, 2002). Lazarus and Folkman (1984) define coping as “*constantly changing cognitive and behavioural efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person*” (Lazarus & Folkman, 1984, p. 141). Accordingly, coping strategies are closely related to cognitive processes involved in the generation of stress state (Everly & Lating, 2002).

Coping strategies can be categorized into *problem-focused* and *emotion-focused* categories. The person who uses a problem-focused coping strategy tries to find information about the problem at hand and searches for possible existing solutions to overcome that problem. In this way, the individual will be able to alter his/her problematic relationship with the environment in a practical way by changing either himself/herself or the environment (Lazarus, 2006).

In contrast, in an emotion-focused coping strategy, the individual is more involved in regulating his/her emotions, which have risen from exposure to a stressful situation, rather than openly encountering the reality and attempting to alter it. Such emotion-regulating strategies may include avoidance (not thinking about the stressful stimuli) or reappraisal. By adopting a reappraisal strategy, the individual can modify his/her emotions by altering the meaning of his/her relationship with a challenging stressful situation (Lazarus, 2006).

Lazarus (2006) holds that the concepts of stress, emotion, and coping are interconnected, constituting one conceptual element in which stress and coping can be secondary to the emotion concept. Therefore, separation of these concepts may draw us away from a realistic perception of the natural configuration of these phenomena.

Nevertheless, several other researchers believe that coping does not include all the possible reactions to stress, but is merely one of them (Keil, 2003). *Coping mediator*s are classified into the following concepts:

- Coping Style
- Coping Effectiveness
    - Effective Coping
    - Ineffective Coping

6.4.2.4 Personality Mediator

Several researchers (e.g. Vollrath, 2001) have emphasized the importance of the integration and systematic linkage of personality factors with stress response. The association between personality characteristics and stress commenced with investigations on how the personality trait of *neuroticism* (Eysenck & Eysenck, 1969) and *type A personality* (Friedman & Rosenman, 1974) affect an individual’s vulnerability to stress response. Other investigators have underlined the central role of personality factors in person’s appraisal of certain stressful situations (Lazarus, 1990). Lazarus (2006) holds that psychological stress is neither a mere effect of the environment nor is caused solely by personality attributes, but a product of the particular relationship (transaction) between the person and his/her environment. He rebuts the psychological concepts of *personality trait* and *coping disposition* as they miss specific context and predictive value (Lazarus & Launier, 1978), are too static, universal, and reductionistic (Lazarus & Folkman, 1984).

On the contrary, the impact of some personality traits on the generation and promotion of stressful situations has been outlined by other studies (Cantor & Zirkel, 1990). For example, studies in the domain of personality psychology suggest that, in the face of stressful situations, individuals with certain personality traits such as neuroticism and *trait anxiety* are more likely to respond with negative emotional reactions of anxiety (Eysenck & Eysenck, 1985).

Furthermore, the *interactional model of anxiety* (Endler, 1975) suggests that an individual's *state anxiety* escalates only when there exists a thematic match between the dimension of his/her *trait anxiety* and the type of perceived hazard in a certain situation. For example, a person whose trait anxiety is high with respect to physical peril would express fearful behaviour only when s/he encounters a physically perilous situation. Or individuals with the trait of neuroticism may become anxious in the face of interpersonal conflicts, but not in other circumstances (Suls, Green, & Hillis, 1998) (Vollrath, 2001).

At the same line, the *stress perception* hypothesis proposes that those with a general tendency to experience high negative affect, compared to low negative affect, are more vulnerable to interpret incidents as stressful, and consequently, express negative emotional reactions (Engelhard, van den Hout, & Kindt, 2003). In a similar manner, some personality dispositions such as *hardiness* have been shown to contribute to the development of PTSD symptoms in at-risk individuals (King, King, Fairbank, Keane, & Adams, 1998).

Moreover, Millon's (1996) *biosocial learning theory of personality* postulates that, because individuals have different coping strategies, reinforcement patterns, needs, and concerns, different personality styles are vulnerable to different sources of stress (Millon & Davis, 1997).

In contrast, other personality characteristics such as *conscientiousness* (Friedman et al., 1995), *optimism* (Scheier & Carver, 1985), *self-efficiency* (Bandura, 1978), and *sense of coherence* (Antonovsky, 1993) seem to buffer the individual against experiencing high levels of stress due to their promotion of one's stability, effective adjustment, resilience, positive evaluation, and growth (Friedman et al., 1995; Vollrath, 2001).

HSO *personality mediators* include a category of personality traits (styles) in addition to two other categories specifying some investigated *stress-sensitive* and *stress-resilient personality traits* as to individuals' vulnerability to stress response and effects:

- Personality Trait
- Stress-Sensitive Personality Trait (e.g. Trait Anxiety, Neuroticism, Perfectionism)
- Stress-Resilient Personality Trait (e.g. Conscientiousness, Optimism)

6.4.2.5 Developmental Mediators

Developmental mediators constitute another important element of psychological mediators of human stress response. The role of developmental factors in the perception of stress response and the impact of stress experience on development has been addressed by many investigators (e.g. Seiffge-Krenke, Aunola, & Nurmi, 2009). Reportedly, individuals' stress perception and experiences undergo a range of alterations both quantitatively and qualitatively across the lifespan. This can be due to various maturational (e.g. physiological) (Ge, Conger, & Edler, 1996), cognitive (Kopp, 1989), coping and situational changes (Zimmer-Gembeck & Locke, 2007) which occur throughout different stages of one's life.

For example, it was observed that during *adolescence*, individuals are more concerned with issues related to their interpersonal relationships and identity. Conflicts and challenges as to the kind of relationships with parents, mates, or members of the opposite sex are some of the most intense sources of stress during this stage of life (e.g. Seiffge-Krenke et al., 2009).The characteristics and mediating role of other developmental stages (e.g. childhood) in stress experience have been studied by other researchers of this field (e.g. Ryan-Wenger, 1992).

The developmental studies of stress response have been closely followed by studies on coping strategies and their alteration throughout one's life. Having referred to Lazarus and Folkman (1984)'s definition of coping as "*constantly changing*" attempts to manage imposed external or internal demands, Amirkhan and Auyeung (2007) emphasize that coping responses are not fixed and trait-like, but are subjected to alteration across different age periods. For example, with the increase of age, children tend to use more problem-focused and less avoidance coping strategies to manage their stress (Amirkhan & Auyeung, 2007). The developmental mediator class covers different stages of development as well as various positive and negative developmental factors:

- Developmental Stage
  1. Infancy
  2. Childhood
  3. Adolescent
  4. Adulthood
  5. Elderly

- Developmental Factor
  - Negative Developmental Factor
  - Positive Developmental Factor

6.4.2.6 Personal Resource

Personal resources are those features of the individual's life such as *intelligence*, *education*, *wealth*, *social skills*, *supportive family and friends*, *physical attractiveness*, and *health*, which influence his/her appraisal of stressful situations, adoption of coping strategies, and successful adaptation (Lazarus, 2006). Some researchers have also exemplified stress-resistant personality characteristics such as *self-esteem* (Scheier & Carver, 1985) and *learned resourcefulness* (Hobfoll, 2001; Rosenbaum & Smira, 1986) as personal resources.

The HSO, therefore, incorporates the category of *stress resistant personality trait* (from the *personality mediator* class) under the category of personal resources. Different studies show that richness of personal resources reduces individuals' appraised stress and help them deal with adverse situations more effectively (Lazarus, 2006). For example, a study by Rini, Dunkel-Schetter, Wadhwa, and Sandman (1999) demonstrated that pregnant women with higher levels of optimism, mastery, and self-esteem, have lower stress reactions and predicted better birth outcomes such as higher birth-weight babies and longer gestation.

In contrast, shortage of personal resources, such as low levels of social support, is correlated with experiencing higher degrees of psychological distress and stress (Billings & Moos, 1981).

The category of personal resources includes:

- Stress Resistant Personality Trait
- Education
- Money
- Social Skill
- Intelligence
- Physical Attractiveness
- Well-being
- Supporting Family
- Supportive Friend
- etc

6.4.2.7 Individual Life Experience

This class of psychological mediators tap into important negative and positive events and experiences that the individual has experienced throughout his/her past life. Such past experiences can influence a person's current responses to stressful situations. It has been shown that the individual's emotional reactions to taxing stimuli and challenging events are influenced and mediated partly by his/her relational history (Lazarus, 2006). For example, the arousal of anger reactions in parent-child relationships is more influenced by one's history of interpersonal stress than by provoking behaviours (Klos & Singer, 1981).

The mediating effects of an individual's life experiences, particularly *life events*, on current stress reactions have been particularly studied by researchers investigating the development of depressive disorders in vulnerable individuals. For example, Brown and Harris (1978) demonstrated that the person's past stressful life events, such as the loss of the mother in childhood, partly moderate the effects of recent or current stressful or challenging situations. Hence, it has been emphasized that early life adversities can significantly mediate and moderate the effects of proximal stressors on the development of depressive symptoms (Hammen, 2005).

Early life stressful events can also contribute to the generation of higher levels of stress in adult life. For example, the experience of neglect or abuse in women's early childhood was associated with the occurrence of more chronic stressors such as relationship stressors in their later stages of life (Bifulco, Bernazzani, Moran, & Ball, 2000).

Another aspect of life experiences relates to one's *history of psychological problems*. Research on the potential risk factors of stress-related disorders indicates that past experiences of psychological disorders increase the likelihood of PTSD development in vulnerable individuals (Yehuda & Wong, 2007).

Furthermore, it has been discussed that the individual's *social experiences* during the *sensitive periods of early development* can determine his/her *stress reactivity patterns* in later stages of development (Gunnar & Quevedo, 2007). The existence or lack of an experience during early periods of development exerts a more severe and lasting impact on neurological functions than do the experiences in later periods of life (Gunnar & Quevedo, 2007).

The HSO category of *individual life experience* covers various types of experience in one's past life including:

- Past Experience
    - Abuse History
    - Early Separation
    - History of Psychological Problem
    - Failure Experience
    - Relational History
    - Trauma History

- Social Experience
- etc

6.4.2.8 Gender Related Mediator

Stress response and its management through the adoption of various types of coping strategies can also be mediated by *manhood* or *womanhood* characteristics (Seiffge-Krenke et al., 2009). Some studies indicate that, in the face of stressful situations, females tend to express more active coping patterns such as support-seeking behaviours (Billings & Moos, 1981). Women also show more emotional reactions to stressful agents and prefer to talk about their problems (La France & Banaji, 1992), whereas, men are likely to either confront a challenging situation or deny its existence (Stone & Neale, 1984).

It seems that women are more susceptible to the detrimental effects of stressors. For example, it has been indicated that females are more likely to develop depressive symptoms after the experience of stressful life events (Maciejewski, Prigerson, & Mazure, 2001). Moreover, several studies show that vulnerable women are more prone to developing *Acute Stress Disorder* and PTSD (Yehuda & Wong, 2007). Women also appear to be more sensitive to negative happenings in their social relationships and more susceptible to becoming stressed over the sufferings of others (Kawachi & Berkman, 2001).

The class of gender-related mediator incorporates two categories of:

- Manhood
- Womanhood

6.4.2.9 Relationship Mediator

The type and quality of an individual's relationships is another significant mediator of his/her stress response. The category of relationship mediator covers a wide range of *family* *relationships* (e.g. *parent-child relationships*, *couple relationship*), *peer relationship*, as well as the quality of these relationships as to, for instance, their security or insecurity.

Neurobiological and developmental studies indicate that infants' level of cortisol secretion in response to stressful situations is influenced by the attendance and responsiveness of the attachment figures (Gunnar & Donzella, 2002; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996). Infants who enjoy having a secure relationship with their caregivers, although they may direct their crying at the attachment figure, do not show signs of cortisol augmentation. On the contrary, insecure and unsupportive relationships can increase HPA axis activation, cortisol secretion, and heart rate (Spangler & Schieche, 1998) (Gunnar & Quevedo, 2007).

Couple relationship is another type of relationship which can moderate the effects of stress reactions. It has been indicated that having positive emotional relationships among partners can buffer against the effects of life stresses (Ryff & Singer, 2000).

Some studies have addressed the impact of peer relationships on individuals' stress response. For example, the challenge of getting engaged in social interactions with peers can escalate the basal cortisol level of children (Gunnar & Donzella, 2002). Less socially competent children who have difficulty regulating their negative emotions tend to maintain higher levels of cortisol secretion during the time spent with their peers (Dettling, Gunnar, & Donzella, 1999). Moreover, peer-rejected and lonely adolescents display the same pattern of high cortisol generation (Adam, 2006).

The following includes the sub-classes of the relationship mediator class:

- Family Relationship
    - Parent-Child Relationship (e.g. Secure Relationship, Insecure relationship)
    - Couple Relationship
- Peer Relationship
    - Peer Acceptance
    - Peer Rejection

Figure 6.4 illustrates the concepts related to the class of psychological mediator.

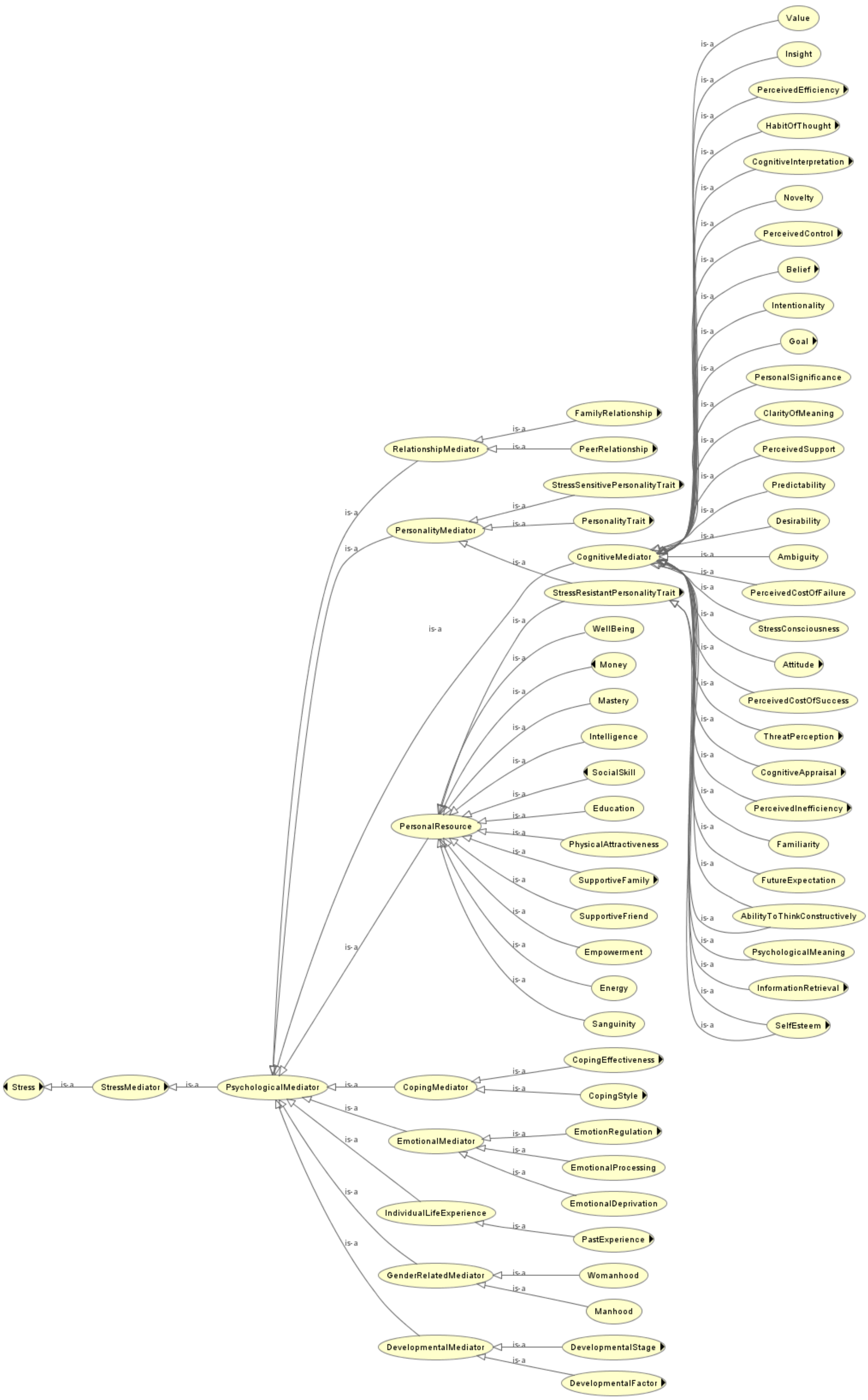

Figure 6.4. Psychological Mediator

6.4.3 Situational Mediator

The role of situational factors as mediator between the stressful agents and human's stress response has been particularly underlined by investigators who have illustrated how situational circumstances can influence the individual's adoption of a certain type of coping strategy in the face of stressors (Terry, 1991). Given that the appropriateness and effectiveness of choosing a coping tactic is relative and depends on the type of adverse situation encountered (Mahat, 1997), people are inclined to apply different coping strategies across various situations (Keil, 2003).

*Situational mediator*s fall into two general categories of *social mediator*, and *temporal mediator*. Social mediators include various types of *socioeconomic* and *cultural* conditions.
Concerning socioeconomic conditions, research has shown that deprived inhabitants of poor societies tend to evaluate their present and future circumstances in a negative way, thereby becoming more vulnerable to the effects of stressful events (Kopp, Skrabski, & Szedmák, 1998). Furthermore, the existence of disadvantageous conditions such as social inequality and social exclusion in one society has been found (Waitzkin & Magana, 1997) to be the cause of many traumas. The onset, course and consequences of traumas can be affected by the individual's cultural and social structures. According to several researchers, social injustice has been revealed as a main precursor to people's distress and agony (Pedersen, 2002).

Another aspect of social mediators relates to the role of cultural features in shaping human behaviour and appraisal in the face of different stressful situations. Studies on cultural aspects of well-being have discussed that different cultures might focus more either on negative or on positive outcomes of their life events, resulting in some cultures promoting more levels of subjective well-being than do other cultures (Diener, Oishi, & Lucas, 2003).

Temporal mediators include factors such as duration, imminence, or the timing of stressful events in one's life and their influence on stress response. For example, people might be sensitive to different sources of stress at different points in their lives (Lazarus, 2006). Also, there are some views holding that execution of some coping strategies has more consistency across the time. For example, implementation of positive reappraisal as a coping strategy to decrease negative emotions is more consistent across different times and situations than is the adoption of support-seeking strategies, as the latter is highly situation-dependent (Lazarus, 2006).

Situational mediators (Figure 6.5) cover the categories of:

- Social Mediator
  - Socioeconomic Mediator
  - Cultural Mediator
- Temporal Mediator
  - Harm Duration
  - Harm Imminence
  - Societal Period (Lazarus, 2006)
  - etc

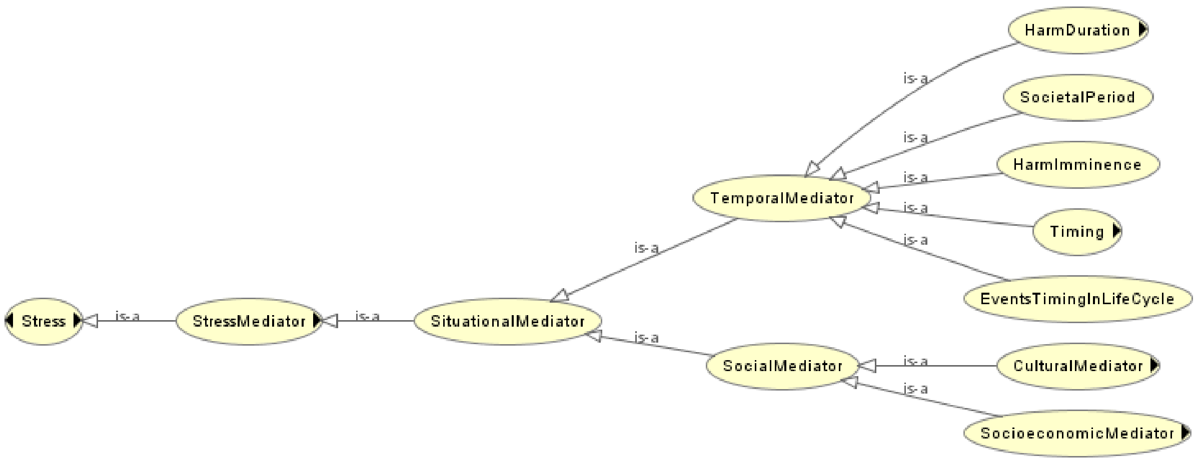

Figure 6.5. Situational Mediator

Figure 6.6 represents the higher-level categories of stress mediator sub-ontology.

Figure 6.6. Stress Mediator

6.5 Stress Response

The term *stress response* implies the concept of *stress*, in its general sense, as is broadly used by both psychologists and physiologists. Since Selye's (1936a) introduction of the term stress to medical and psychological research, thousands of research papers have been written on this phenomenon and its various effects, however, no scientific definition of it has yet been formulated (Goldstein, 1995).

Different theorists and researchers have outlined certain features of stress response as necessary conditions in their definition of stress. For example, Selye by his proposal of *stress syndrome* and its signs (i.e. adrenal hypertrophy, gastric ulceration, and thymicolymphatic involution) (1936b) and *General Adaptation Syndrome* (GAS) (Selye, 1950a) highlighted the role of the HPA axis in generating a *non-specific* stress response. Levine and Ursin (1991) incorporated *adaptive biological responses* into the characterization of stress. Chrousos and Gold (1992) defined stress as "a *state of disharmony, or threatened homeostasis*" which can elicit both stressor-specific and non-specific responses. Goldstein (1995) points to the mismatch between the individual's expectations (whether genetically programmed or obtained through learning or deduction) and his/her appraisal of the environment (external or internal) as necessary conditions for the production of compensatory stress responses. And McEwen (1998) integrated the concept of *allostasis* to describe the adaptation process of the organism in the face of different stressors (Pacák & Palkovits, 2001).

It seems the definition of stress evolves as our knowledge of its underpinning mechanisms, mediators, and effects progresses. The HSO brings together various characteristics and features of human stress response under the category of *stress response* in order to portray different aspects of this phenomenon including:

- Stress Response Manifestation
- Stress Response Duration
- Stress Response Normality
- Stress Response Adaptational Feature

6.5.1 Stress Response Manifestation

Human stress response has various *physiological*, *behavioural,* and *psychological* manifestations. There have been discussions as to whether various stressors induce non-specific physiological stress response or the organism manifests specific stress responses in reaction to each particular stressor. Cannon (1939) initially noticed that the organism shows different homeostatic reactions to different disturbing agents such as hypoxia, excessive heat, or cold. Having outlined the significance of various psychological as well as physiological responses during stress (though he never used the term *stress*), Cannon questioned the adaptive functionality of a non-specific stress response (Cannon, 1914, 1929; Pacák & Palkovits, 2001). However, afterward, Selye emphasized the non-specificity of the stress response (Selye, 1936a). Selye, although admitted that different stressors do not necessarily precisely educe the same stress response in different individuals; rather, he held that an operational definition of stress response must rule out those physiological alterations which are caused by only one or a limited number of stressors (Selye, 1985). Therefore, in Selye's view, the secretion of ACTH can elicit a non-specific response during all stages irrespective of the type of stressor (Selye, 1950a). Selye (1976b) later identified two types of reactions elicited in response to most of the stressors: (1) a general stress response (characterized by the discharge of ACTH and adrenal corticosterone) which can be produced by all types of stressful agents, and (2) individual stress responses which can be influenced by conditioning mediators, for example the person's genetic predispositions (Pacák & Palkovits, 2001).

However, later researchers observed that the HPA axis does not demonstrate the same pattern of response in the face of different stressor types. For example, Mason (1975) criticized Selye's notion of stress syndrome, indicating that the HPA activity may augment, reduce, or remain unchanged in reaction to different stressful stimuli. Instead, he underlined the role of psychological factors such as emotions (e.g. fear or anxiety) as the main determiners of alike neuroendocrine responses to stressors of various types (Goldstein, 1995). Mason et al. (1976) in a significant study to control the confounding effects of the two levels of analysis (i.e. psychological versus physiological), managed to keep the physical stressors separate from the psychological ones. The results of their study demonstrated that physical stimuli have the minimal or no effects on the secretion of corticosteroids, whereas perceptions of harm or threat (psychological stressors) have a significant effect on their activation. Therefore, they concluded that the elevation of adrenal cortical alterations of the GAS highly depends on the individual's conscious perception or appraisal of threatening stimuli (Lazarus, 2006).

Recent genetic and neurophysiological studies point to the existence of heterogeneity and specificity in induced neuroendocrine and even genetic responses to different types of stressors (Pacák & Palkovits, 2001; Senba, Matsunaga, Tohyama, & Noguchi, 1993).

In his cognitive theory of stress and coping, Lazarus (1984a, 2006) criticizes the analytic reduction of psychological stress into its supposedly physiological elements, holding that the neurophysiological and psychological concepts must be dealt with at different levels of explanation which cannot be translatable to one another.

Stress response manifestations (Figure 6.7) are categorized as:

- Physiological Stress Response
- Behavioural Stress Response
- Psychological Stress Response

6.5.2 Stress Response Duration

In terms of duration and length, stress response can be classified into two types: *acute stress response* and *chronic stress response*. Acute stress response refers to the organism's physiological, emotional, and behavioural processes which are elicited in reaction to intermittent and time-limited exposure to acute stressors (Pacak & McCarty, 2007). The elicited physiological processes in an acute stress response help the organism to redirect and mobilize energy consumption across different organs, and activate or inhibit particular organs, in order to prepare certain related organs (e.g. muscles) to expose and challenge further taxing or threatening stimuli (Pacák & Palkovits, 2001). In contrast, chronic stress response implies the organism's physiological, behavioural, or emotional reactions to the impact of prolonged, constant and unrelenting taxing demands such as stressful roles at work (Lazarus, 2006; Phillips et al., 2007).

Acute and chronic stress responses may exert different effects on physiological and psychological systems. For example, while acute stress response may escalate plasma levels of *Growth Hormone* (GH), chronic stress response inhibits the pituitary secretion of GH (Chrousos, 1998). *Stress response duration* includes:

- Acute Stress Response
- Chronic Stress Response

6.5.3 Stress Response Normality

Human stress response can also be classified as either *normal* or *abnormal* according to its functionality, adequacy, and effectiveness for the organism's adaptation and survival. Inadequate, excessive, hyper-reactive, and prolonged stress responses which hinder the restoration of homeostasis and lead to diseases of adaptation (Pacak & McCarty, 2007; Selye, 1976b) are considered as abnormal (Charmandari et al., 2005). Abnormal prolonged stress responses may cause the organism to consume its resources without being able to recover them adequately, thereby experiencing physiological and behavioural problems, namely, *allostatic load* (McEwen, 2000). In contrast, a normal stress response facilitates effective and adequate adaptation and survival of the organism (Selye, 1976b). *Stress response normality* is categorized as:

- Normal Stress Response
- Abnormal Stress Response

6.5.4 Stress Response Adaptational Feature

Claude Bernard (1854), one of the earliest contributors to the study of stress, proposed the concept of *milieu intérieur*, i.e. the *constancy of the internal environment*, which initiated future research on the adaptational aspect of stress. Bernard had discovered the role of insulin deficits in some physiological disorders such as diabetes or mental confusion. This discovery led physiologists and biologists to consider the concept of *homeostasis* (Cannon, 1939) through which the organism supposedly maintains its internal balance, e.g. the right amount of required sugar or oxygen, in order to survive. The ideas of Claude Bernard indirectly affected later approaches to adaptive processes and survival. For example, adaptive actions such as shelter seeking and flight were viewed as mechanisms to ensure the survival of organism. However, at the same time, it was observed that the expression of such survival-oriented actions and efforts may disrupt the organism's state of homeostasis (Lazarus, 2006).

The concept *homeostasis* as "*the coordinated physiological reactions which maintain most of the steady states in the organism*" (Cannon, 1929, 1939) was primarily introduced by Cannon to address the organism's stress-induced deviation from its stable state. He focused particularly on the sympathetic nervous system and its adaptive and homeostatic functions in re-establishing the disturbed state of homeostasis caused by stressful agents. Canon noticed that in order to respond to a threatening situation through a fight or flight response, the organism must initially mobilize its bodily resources. However, such energy mobilization, if continued for a long term, may bring about intense and long-lasting feelings of anger or fear, which in turn, can be stressful and detrimental to the body (Lazarus, 2006).

Subsequent to Bernard's and Canon's discoveries, Hans Selye (1956, 1976b) formulated his prominent theory of stress in physiology. Selye explained the physiological processes through which the body mobilizes its resources to respond to threatening and harmful situations. He postulated the notion of the *General Adaptation Syndrome* (GAS) to describe the neuro-chemical and physiological alterations undergone by the body in order to defend against noxious stimuli. He described three stages of the GAS as:

1. *Alarm reaction.* In the first stage, the encountered harmful stimulus educes neuro-chemical and hormonal processes in the body.

2. *Resistance.* If the stressor exposure continues, in the next stage, the organism mobilizes and concentrates its resources on defending itself against the enduring exposure to the stressor. In this stage, the body may respond with the inflammation of injured tissues, isolating those tissues from the rest of the body. This process helps the body contain the harm and deal with it locally without damaging other sections. This swelling and inflammation then will be recovered and healed with anti-inflammatory adrenocortical hormones. The resistance stage is a catabolic stage, consuming bodily resources in contrast to anabolism which restores those resources.

3. *Exhaustion.* This stage would occur only if the intense severe stressor continues for a long time beyond the bearing capacity of the organism, resulting in the failure of bodily repositories. The prolongation of intense taxing stressors beyond a certain measure, at this stage, may cause the over-depletion of bodily repositories and even death (Lazarus, 2006).

The organism's adaptation response takes on various physiological and behavioural features. For example, physiological adaptation may incorporate various bodily reactions of *enhanced* *analgesia*, *core temperature elevation*, *oxygen concentration*, and *cardiovascular tone increase* (Charmandari et al., 2005). Behavioural adaptation includes different behavioural responses of *alertness*, *focused attention*, *fight*, *flight*, etc (Charmandari et al., 2005). The *stress response adaptational feature* contains several of the abovementioned aspects of human adaptation response plus other related concepts such as *adaptational failure* or *adaptational transaction* (Lazarus, 2006):

- Physiological Adaption
- Behavioural Adaptation
- Adaptational Transaction
- Adaptational Failure

Figure 6.7 illustrates the HSO sub-ontology of stress response.

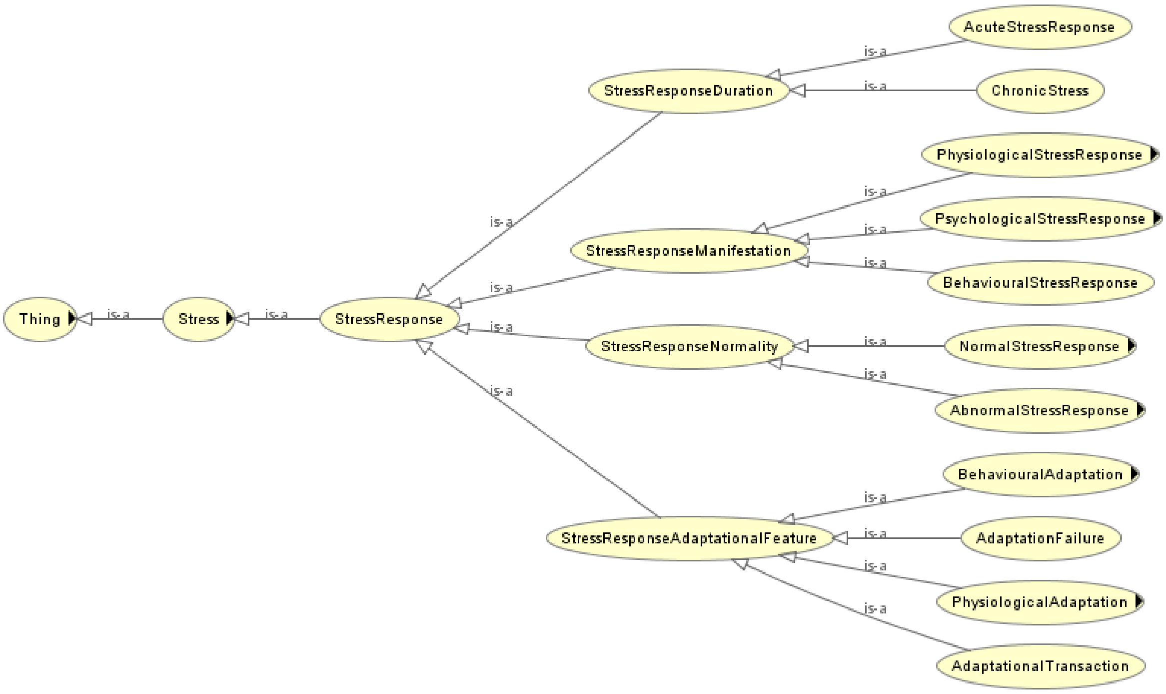

Figure 6.7. Stress Response

6.6 Stress Effect

Stress can produce a broad range of neurophysiological, physiological, and psychological response mechanisms and exert transitory or long-lasting impact on various organs and psychological functions such as cognition, emotion, memory, learning, attention, interpersonal relationship, personality, and in general, well-being of individuals. The *stress effect* sub-ontology incorporates diverse functional and structural effects of stress response on human into the following three subclasses (Nasiri Khoozani & Hadzic, 2010):

- Biological Alteration
- Psychological Alteration
- Stress-related Disorder

6.6.1 Biological Alteration

Stress response can cause various physiological and neurophysiological alterations. In regard to physiological alterations, there is a great deal of evidence, indicating different effects of stress on various *physiological functions* and *musculoskeletal reactions* (e.g. *muscle vasodilatation*) (Gunnar & Quevedo, 2007). For example, stress can interfere with the release of insulin, thereby making the individual vulnerable to developing diabetes (See Surwit, Schneider, & Feinglos, 1992 for review). Or stress reactions can cause changes in blood flow, contribute to blood vessel constriction, enhance cardiac output and heart rate, and result in a variety of metabolic modifications (e.g. *hyperphagia*) (Gunnar & Quevedo, 2007).

In terms of neurophysiological alterations, it has been demonstrated that long-term stress reactions underpin the *hypersensitivity* of the limbic system contributing to the consequent arousal disorders (Monroe, 1982). There are a number of pathways through which stress exerts its neurophysiological impact on the limbic system function and structures (Everly & Lating, 2002). Stress can:(1) contribute to the augmentation of neuromuscular efferents excitation, (2) diminish the density of inhibitory neurotransmitters and/or receptors (Cain, 1992), (3) trigger excitatory neurotransmitters located in the limbic circuits (Post, Rubinow, & Ballenger, 1986), (4) enhance the morphological constructions of amygdala (Cain, 1992), and (5) induce proprioceptive signals, thereby, bombarding the limbic circuits (Gellhorn, 1964) (Everly & Lating, 2002).

In terms of genetic modifications, glucocorticoids can cause some modifications in gene transcription and genomic processes which may bring about alterations in transduction mechanisms (Cain, 1992) as well as changes in brain structure and functioning (Charmandari, Kino, Souvatzoglou, & Chrousos, 2003).

Studies have reported that adolescents' exposure to early and chronic stressful life events may predict changes in their grey matter quantity and neuronal integrity of the frontal cortex, as well as diminution in the mass of anterior cingulated cortex (Cohen et al., 2006). The impact of the exposure to chronic or traumatic stress on particular areas of brain largely depends on the maturation and developmental stage of those brain regions, which vary among different age groups (Lupien, McEwen, Gunnar, & Heim, 2009). There is also evidence suggesting that chronic stress contributes to the attenuation of the frontal lobe and hippocampus, but increases the size of the amygdala (Lupien et al., 2009; Mitra & Sapolsky, 2008).

The HSO category of biological alterations (Figure 6.8) includes:

- Physiological Alteration
  - Physiologic Function Alteration
  - Muscle-Skeletal Reaction
- Neurophysiological Alteration
  - Nervous System Alteration
  - Norendocrine Activity Alteration
  - Genetic Alteration

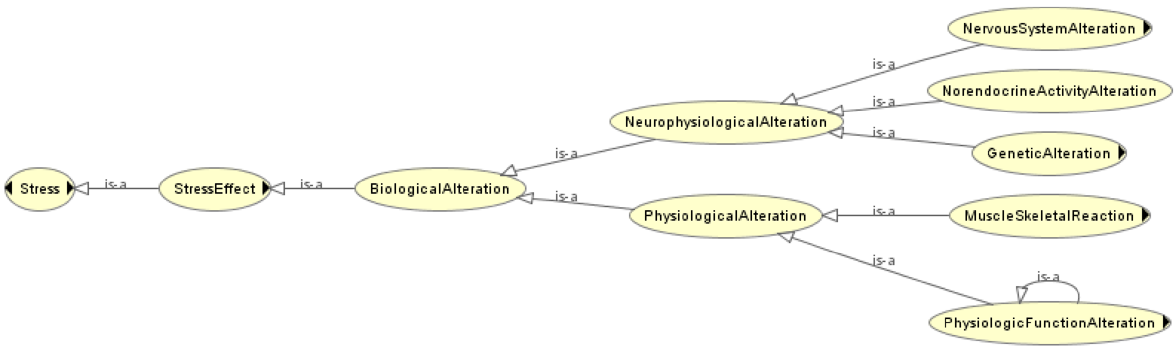

Figure 6.8. Biological Alteration

6.6.2 Psychological Alteration

Psychological alterations consist of different aspects of human psychology which are likely to be influenced by the effects of stress. These include:

- Cognition Alteration
- Emotion Alteration
- Memory and Learning Alteration
- Attention alteration
- Interpersonal Relationship Alteration

6.6.2.1 Cognition Alteration

Various effects of stress on cognition and information processing have been addressed by a number of theories. For example, it has been indicated that the person exposed to a stressful stimulus tends to narrow his/her attention on the encountered stressful agent, paying less attention to other adjacent stimuli, in order to concentrate on the stressor and be prepared for necessary reactions. This phenomenon is called *perceptual narrowing* or *perceptual tunnelling* (Baddeley, 1972; Wickens & Hollands, 2000).

The *cognitive tunnelling* theory holds that the cognitive processing in the stressed individual is apt to retrieve and concentrate on the well-known and well-practised memory materials. The stress-induced modifications in *retrieval thresholds* and declarative processing make the individual more inclined to retrieve and implement only the well-known and reliable stored information when facing a stressful situation (Wickens, Barnett, Stokes, Davis, & Hyman, 1989).

It has also been postulated that stress can result in a recurring course of *cognitive activation* (Gellhorn, 1964). The intervening effects of such repetitive and dysfunctional cognitive processing are particularly highlighted by experimental studies on the role of mediating factors contributing to the development and continuation of PTSD symptoms (Foa &

Rothbaum, 1998). For example, victims of severe stressful traumas have a tendency to appraise the world as an excessively insecure environment. Experience of traumatic events can also cause such patients to underestimate their own capability and resources to manage encountered stressful circumstances (Foa & Cahill, 2001).

Psychological *decompensation* (Lazarus, 2006) is another stress-induced dysfunctional cognitive processing. Decompensation implies the decline of cognitive or emotional functionality in a strained individual trying to tackle a stressful situation or psychiatric disorder (Menninger, 1945).

It has been indicated that chronic stress (e.g. prenatal maternal stress) can engage different brain regions such as the hippocampus resulting in their structural changes such as reduced volume of the hippocampus (Mirescu, Peters, & Gould, 2004). Decreased hippocampus neurogenesis in schizophrenic individuals is reportedly associated with a variety of deficits in cognitive performance such as *reduced response speed*, *decreased response accuracy*, *poor executive function*, *poor verbal knowledge*, and *deficient abstract capacities* (Walker et al., 2008).

Chronic stress can also produce a deleterious impact on cognitive functions of the prefrontal cortex, such as reduced *creativity* and *problem solving* ability (Beversdorf, Hughes, Steinberg, Lewis, & Heilman, 1999).

6.6.2.2 Emotion Alteration

Stress is also strongly associated with the arousal and course of different types of emotions. Stress and emotion, according to Lupien et al. (2007) share some common characteristics, although they are not exactly the same phenomena. Stressful experiences can elicit various emotions such as *surprise*, *fear* or *joy*. Conversely, elevation of certain emotions can cause feelings of stress in the individual. The differentiation of emotion from stress, according to this view, rests on the assumption that every stressful experience would necessarily educe a particular emotion, but not all types of emotions in all situations can cause feelings of stress in individuals (See Lupien et al., 2007 for a review).

Lazarus (2006) holds that stress, emotion, and coping are interconnected phenomena, forming one conceptual entity in which concepts of stress and coping are secondary to the emotion concept. Accordingly, the arousal of an emotion type is determined by the individual's evaluation and appraisal of the encountered events. For example, at the stage of secondary appraisal, evaluation of one's coping potentials, future expectations, and his/her beliefs about who should be blamed or credited for an outcome, can determine his/her type of elicited emotion. Furthermore, emotion alterations over the process of dealing with a stressful situation follow the shift of undertaken coping strategies. With this respect, problem-focused coping strategies and positive reappraisal turn negative emotions into positive ones, while emotion-focused coping tactics such as avoidance result in one experiencing negative emotions (Lazarus, 2006). Nevertheless, other researchers (Phelps, 2006; Zajonc, 1984) believe that a stressor can elicit amygdala-based emotions prior to and independent from one's cognitive appraisal.

According to another stream of research, people's daily *mood fluctuations* are induced by their experience of stressful life events (Bolger, DeLongis, Kessler, & Schilling, 1989).

6.6.2.3 Memory and Learning Alteration

Research into the effects of stress on learning and memory was initially inspired by earlier studies on the effect of glucocorticoid therapy on psychotic symptoms (steroid psychosis) (Clark, Bauer, & Cobb, 1952; Lupien et al., 2007). Memory and learning functions can be influenced by stress response in different ways. The differential effects of stress on memory depend on the interaction of various factors including the type of stressful agent, gender-related mediators, time-related factors, and the emotional excitement of the material which is going to be remembered. For example, the experience of stressful feelings ensuing to a learning situation promotes *memory consolidation* (Roozendaal, 2000), while exposure to a stressful situation, and its subsequent escalated cortisol levels, previous to a memory examination task is likely to interfere with *memory retrieval* functions (Buchanan & Tranel, 2008).

The observed effects of stress on memory and learning are consistent with the discoveries indicating the existence of a high concentration of glucocorticoid receptors in the hippocampus region, where memory and learning processes occur. For example, it has been indicated that consumption of acute doses of glucocorticoids can restrict the function of *declarative memory* as this type of memory is managed by the hippocampus (Lupien & McEwen, 1997). Moreover, glucocorticoids can negatively affect people's capability to retrieve stored information (De Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000). Along the same line, experience of severe stressful events during early stages of development is likely to result in enduring *learning deficits* throughout the life span (Lemaire, Koehl, Le Moal, & Abrous, 2000).

W*orking memory* functions may also be disrupted by the augmented levels of glucocorticoid (Young, Sahakian, Robbins, & Cowen, 1999). Stress and feelings of worry can consume working memory resources resulting in its diminution (Lupien, Gillin, & Hauger, 1999; Wickens, Gordon, & Liu, 1998). This type of memory which is controlled by the frontal areas is responsible for the maintenance of a small piece of information during a short time while that piece of information is being processed (Baddeley, 1995). In contrast, data suggest that the secretion of stress hormones during the retrograde experience of emotionally-loaded events augments the long-term memory for those past events (Lupien et al., 2007). Since the mechanisms of emotional processing are controlled partly by the frontal lobes, it has been proposed that the effects of glucocorticoids on those regions of the brain contribute to modifications in the *emotional memory* (Buchanan & Lovallo, 2001).

Other researchers have addressed the potential positive effects of stressful experiences on memory and learning (Lupien et al., 2007). For example, enhanced levels of cortisol at the time of learning and information encoding foster the recall of emotionally-arousing past scenes (Buchanan & Lovallo, 2001).

6.6.2.4 Attention Alteration

A number of studies have addressed the potential effects of stress response on attention modification (e.g. Born, Kern, Fehm-Wolfsdorf, & Fehm, 1987). Some studies postulate that behavioural arousal can be induced by the innervation of Type I receptors in response to stressors, thereby increasing the individual's attention and vigilance (Oitzl & De Kloet, 1992). Furthermore, exposure to a stressful stimulus causes the person to narrow his/her attention, concentrating on the source of stress and paying less heed to other surrounding stimuli (Baddeley, 1972). However, performance of tasks of *selective attention* (e.g. telephone search task) can be interrupted by enhanced glucocorticoid levels during exposure to chronic stress (Lupien et al., 1994). Stressful situations (e.g. student exam periods) can also decrease individual' *divided attention*, which is represented in tasks such as telephone searching while performing a counting job (Vedhara, Hyde, Gilchrist, Tytherleigh, & Plummer, 2000). Recent results suggest that stress-induced attentional impairment (e.g. impairment in *attention shifting* or *attentional control*) in anxiety and depressive disorders may be due to dendritic modifications in the medial prefrontal cortex and orbital frontal cortex caused by chronic stress (Liston et al., 2006).

6.6.2.5 Interpersonal Relationship Alteration

Psychological effects of stress are not limited to individual cognitive or emotional processing, but also draw on various aspects of one's social and *interpersonal relationships*. For example, interpersonal and *emotional bonding* between victims of a common traumatic event will flourish and continue long after the experience of that event (Lindy, 1985). However, other aspects of interpersonal relationships such as *intimacy* and *sexual relationships* with a partner may be negatively affected by the deleterious impact of traumatic stress (Escobar et al., 1983).

The category of *psychological alteration* can be seen as a whole in Figure 6.9.

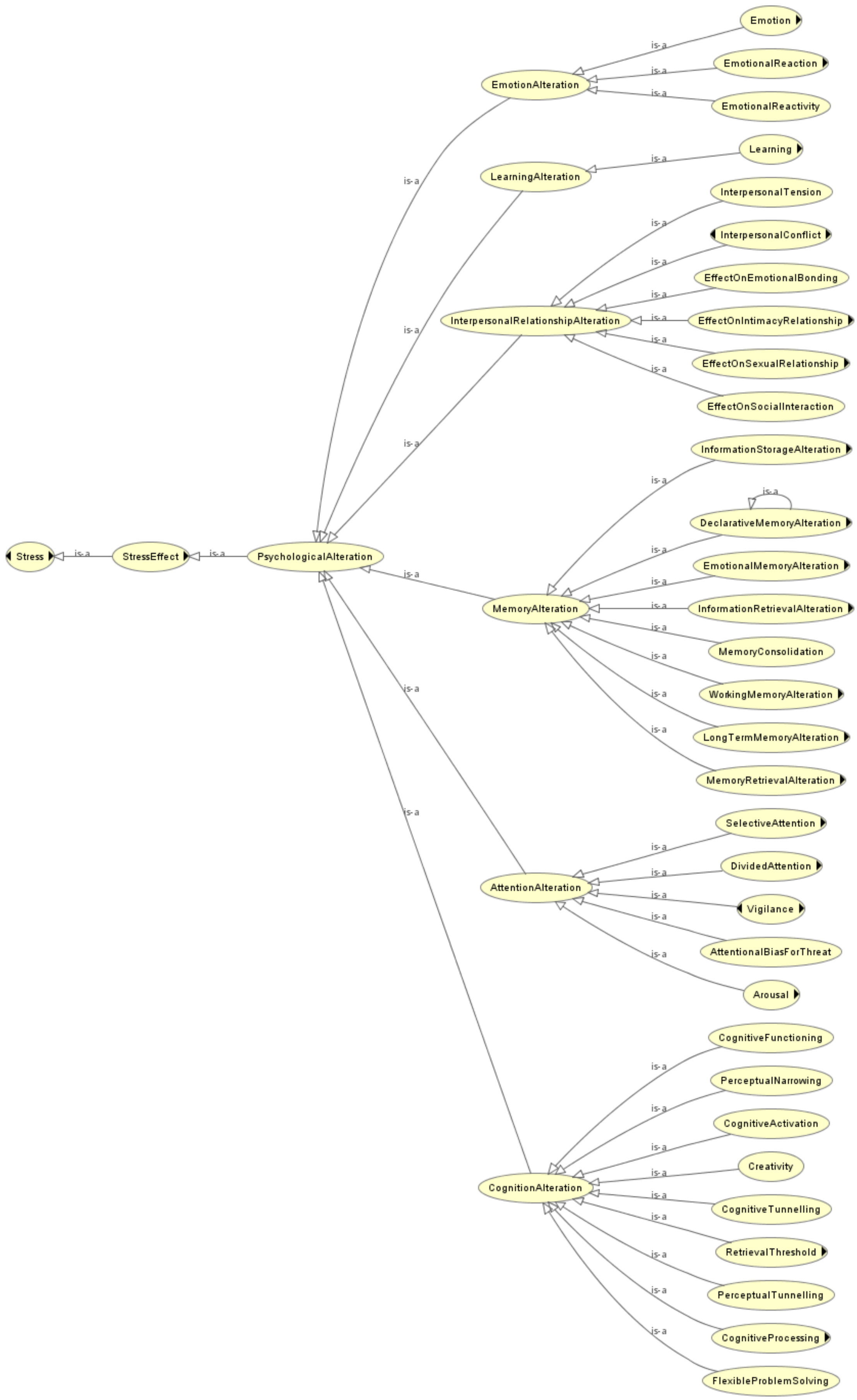

Figure 6.9. Psychological Alteration

6.6.3 Stress-related Disorder

The hyperactivity or hypersensitivity of the limbic system is regarded as a latent factor which induces states of excessive arousal and predisposition to enhanced excitation in response to stressful stimuli. This latent factor is shared by all types of psycho-physiological stress-related disorders (Monroe, 1982). The common hyperarousal feature of all such disorders, places them under the general category of *disorders of arousal* or *psychosomatic disorders* (Everly & Lating, 2002).

Continued exposure to chronic stressors can result in HPA axis hyperactivity, which in turn, increases the individual's susceptibility to the onset and development of stress-related mental disorders (Lupien et al., 2009). Results suggest that the individual's inadequate, excessive, or prolonged physiological or psychological stress response can influence his/her personality development (Chrousos & Gold, 1992), leading to some personality disorders. For example, clinical data has established a significant association between early life traumatic events such as child abuse or disrupted attachment and development of *borderline personality disorder* (Herman, Perry, & van der Kolk, 1989).

Chronic stress can also contribute to the development of various stress-related physiological disorders such gastrointestinal disorders (e.g. peptic ulcer) (Mönnikes et al., 2000) and skin diseases (e.g. rosacea) (Kimyai-Asadi & Usman, 2001).

As can be seen from Figure 6.10, the HSO has incorporated all stress-related disorders, their symptoms and risk factors into three sub-categories of:

- Stress Related Disorder Type
    - Stress Related Physiological Disorder
    - Stress Related Psychiatric Disorder
- Stress Related Disorder Symptom
    - Physiological Symptom
    - Psychiatric Symptom
- Stress Related Disorder Risk Factor
    - Biological Risk Factor

- Psychological Risk Factor
- Environmental Risk Factor

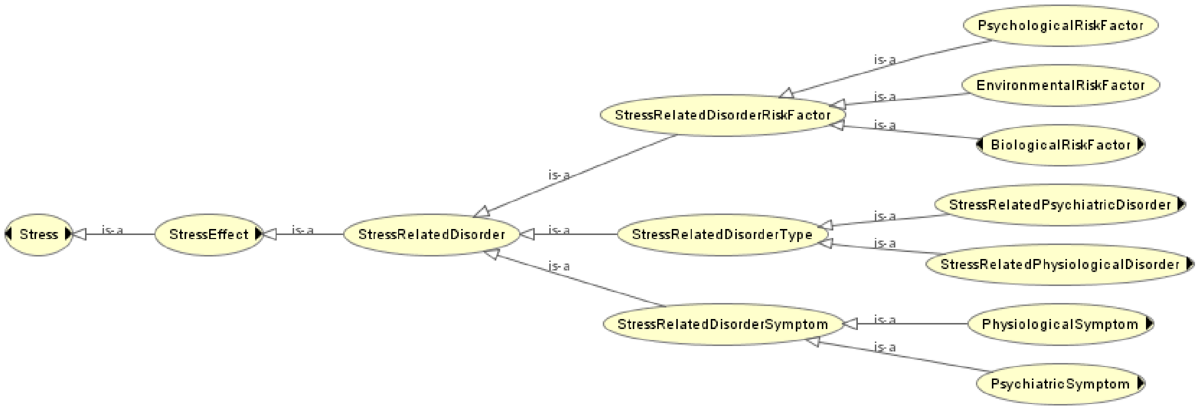

Figure 6.10. Stress-related Disorder

6.7 Stress Treatment

Clinicians and researchers have postulated and developed a range of stress regulation and treatment strategies by use of which over-stressed individuals are likely to manage the detrimental feelings and effects of their stress response in different adverse situations. Non-adaptive stress-response and stress-related disorders can be controlled by different methods including (Everly & Lating, 2002; Nasiri Khoozani & Hadzic, 2010) :

- Psychotherapy
- Pharmacotherapy
- Physiological Technique
- Alternative therapy

6.7.1 Psychotherapy

The aim of *psychotherapy* is to alter individuals' negative affective or cognitive styles, enabling them to develop and promote more positive and functional attitudes in order to manage the encountered stressors as well as the expression of their elicited emotions in an effective way (Frank, 1988). The successful process of psychotherapy depends on a number of psychological and situational factors. For example, it has been discussed that psychotherapy techniques for the treatment of stress-related disorders such as anxiety and depressive disorders must consider the significance of the patient's personality attributes. Accordingly, personality patterns can largely determine the appropriate way in which certain psychiatric conditions can be diagnosed and dealt with (Zinbarg, Uliaszek, & Adler, 2008). Everly (1987) emphasizes that the identification of the *idiosyncratic personologic style* may assist the therapist to uncover patients' psychological stressors, diagnose their chronic stress-induced conditions, and observe the progress, recovery, and responsiveness of stress-related disorders to a prescribed therapeutic strategy.

Various psychotherapy techniques including different methods of *cognitive psychotherapy*, *cognitive-behavioural therapy*, *psycho-dynamic* and *long-term psychotherapy* have been developed for the treatment of abnormal stress responses. For example, cognitive-based psychotherapies (e.g. Beck (1976), Ellis (1977), Meichenbaum (1977)) address the modification of irrational and stress-inducing thoughts and emotions. The basic assumption underlying these therapies is that the patient holds a negative and distorted view of events due to a preponderance of dysfunctional defences and ineffective coping strategies which might be rooted in certain personality traits or habits of thought. The psychotherapist, therefore, aims to uncover such dysfunctional cognitive, motivational, or relational dispositions and amend them (Lazarus, 2006).

Cognitive-behavioural therapies such as *stress inoculation training* (Meichenbaum & Cameron, 1983) aim to equip the individuals with problem-solving abilities which can be effectively used for the management of stressful situations. Other behavioural techniques have outlined the principle of *exposure* (Foa & Kozak, 1986) in the treatment of anxiety disorders. Accordingly, anxiety disorders can be defined as the individual's constant efforts to avoid confrontation with internal or external fear-inducing stimuli. Psychotherapy, hence, must provide the patient with a situation where s/he is encouraged to confront perceptions of such stimuli so that her/his negative emotions can be controlled and amended (Lazarus, 2006).

Recent clinical findings propose that *group cognitive behaviour therapy* can be another effective strategy for the treatment of patients suffering from chronic PTSD (Beck, Coffey, Foy, Keane, & Blanchard, 2009).

Situational factors such as the environment can also affect the process and outcome of psychotherapy. For example, in situations where the environment seems to be a significant determinant of the person's desires, thoughts, and behaviour, the environment modification should be the focus of therapy (Lazarus, 2006).

By and large, most psychotherapy theories agree that the process of amendment and recovery is influenced and determined by the interaction of all cognitive, emotional, motivational, behavioural (coping), and environmental variables. Hence, the integration and compatibility of such variables are considered as key elements in the promotion of mental health and well-being (Fischer & Pipp, 1984; Lazarus, 2006).

Psychotherapy can also draw on the management of stressful crises in people's lives by implementing strategies such as provision of psychological first aid for the victims, promotion of effective coping strategies among sufferers, rehabilitation, and reorganization of victims' personality structure (Lazarus, 2006; Slaikeu, 1990).

The HSO category of psychotherapy (Figure 6.11) has encompassed several sub-classes, each including a number of concepts and instances as follows:

- Cognitive Psychotherapy (e.g. Beck, Ellis, and Meichenbaum Cognitive Therapy)
- Cognitive Behavioural Therapy (e.g. Exposure Therapy)
- Psychodynamic Therapy
- Interpersonal Therapy
- Crises Management

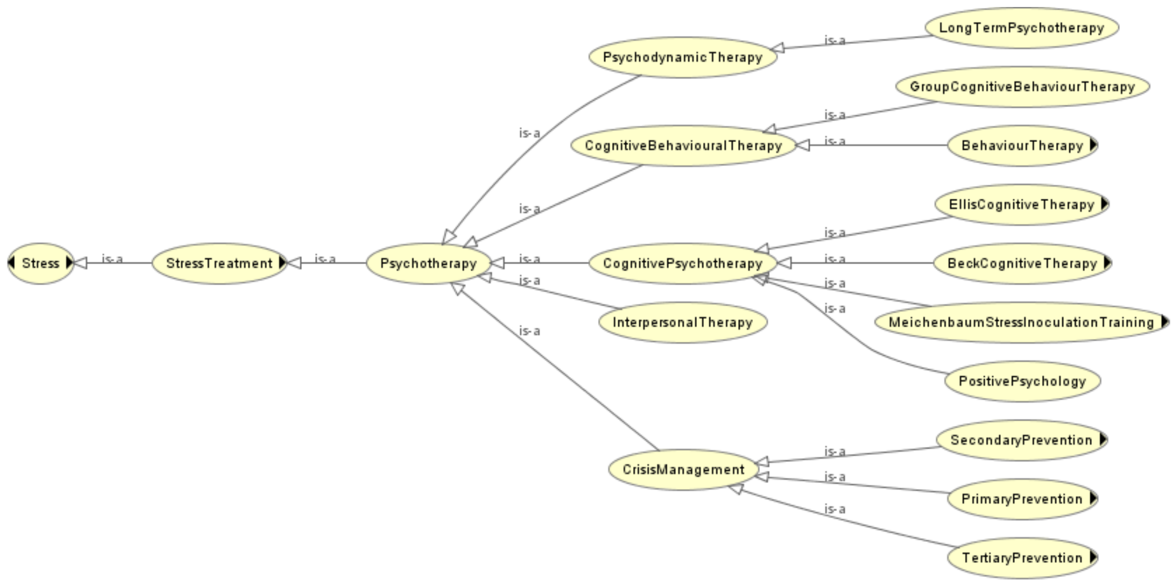

Figure 6.11. Psychotherapy

6.7.2 Pharmacotherapy

In terms of neurophysiological functions, stress-related disorders can be caused by the occurrence of a cycle of physiological positive feedback or a deficiency of inhibitory factors due to over-activation and dysregulation of stress hormones and its consequent imbalanced homeostasis (Everly & Lating, 2002).

In this regard, a broad range of psychiatric medications has been generated to assist patients recover and return to their balanced homeostasis state (Greengard, 1978). However, several recent research reviews indicate that there is no identified specific biological marker of some stress-related disorders such as anxiety disorders (Abramowitz, 2010; Antony & Stein, 2009). Furthermore, prescription of some pharmacologic medications can even interfere with the positive effects of psychotherapy. For example, recent studies suggest that the reduction of glucocorticoid activity induced by anxiolytic medications (e.g. Benzodiazepines) may hamper the process of extinction learning in exposure-based psychotherapies (Otto, McHugh, & Kantak, 2010). These findings are consistent with discoveries demonstrating the significant role of glucocorticoids in augmenting extinction-based learning and emotional consolidation (Lupien et al., 2005). Moreover, inappropriate use of pharmacologic agents can interfere with patients' development and utilization of effective and adaptive coping strategies in the face of fear-inducing situations (Abramowitz, 2010). It has also been emphasized that the individual's beliefs about the existence of a *chemical imbalance* as the underlying cause of his/her anxiety symptoms can weaken his/her feelings of self-efficacy and induce scepticism toward nonmedical therapies (Deacon & Lickel, 2009).

The pharmacotherapy category of the HSO (Figure 6.12) draws on two broad-spectrum classes of *pharmacologic medication* and *pharmacologic effect*. Pharmacologic medication incorporates various families of psychiatric drugs for stress-related disorders including *Benzodiazepines, Antidepressants, Antipsychotics, Miscellaneous Agents,* and *Buspirone* (Everly & Lating, 2002). The class of pharmacologic effect covers various physiological and psychological effects and side-effects caused by pharmacologic medicines:

- Pharmacologic Medication
    - Benzodiazepine
    - Antidepressant
    - Antipsychotic
    - Miscellaneous Agent
    - Buspirone
- Pharmacologic Effect
    - Anxiolytic Effect
    - Hypnotic Effect
    - Muscle Relaxant Effect
    - Sleep Inducing Effect
    - Anti-Convulsant Effect
    - etc

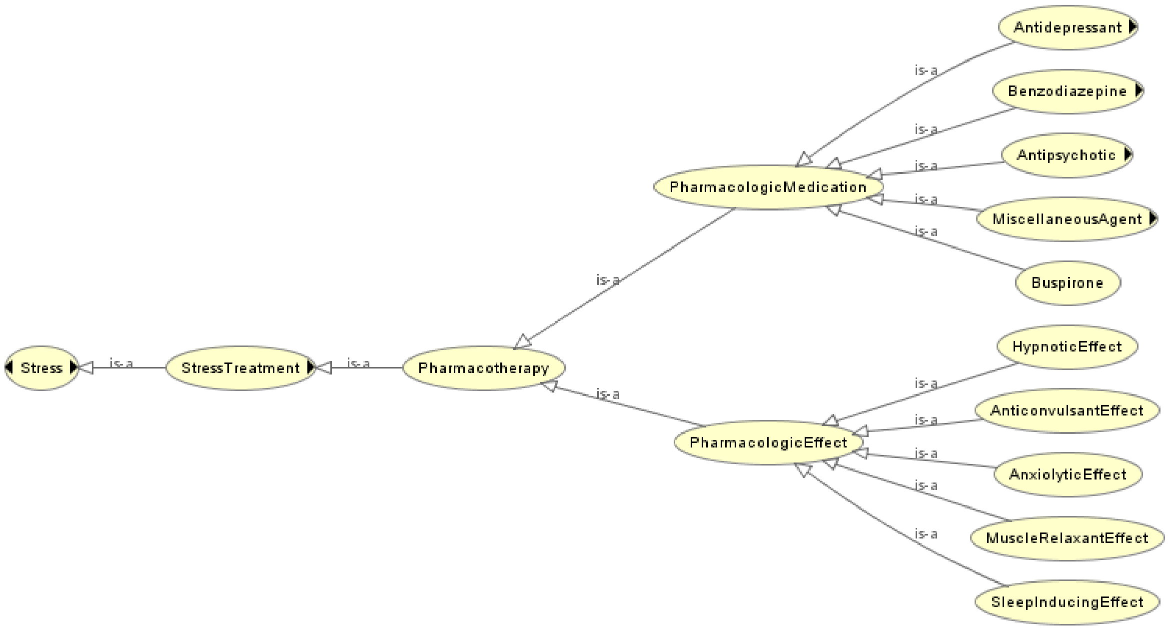

Figure 6.12. Pharmacotherapy

6.7.3 Physiological Technique

The control and attenuation of hypersensitivity and hyper-reactivity of structures within the limbic system has been considered as a potential target of therapy for the disorders of arousal (Benson, Pomeranz, & Kutz, 1984). This method can be implemented through a number of desensitization or relaxation techniques such as progressive relaxation, mantra meditation, presuggestion hypnosis, biofeedback, prayer (Benson, 1983), musculoskeletal therapies such as muscular relaxation, stretching, and massage, or strategies to modify breathing, sleeping, exercise, nutrition, and dietary patterns (Everly & Lating, 2002).

There is some evidence to suggest that attenuation of the cognitive excitation through the effects of relaxation techniques can result in a reduction of ergotropic tone, and consequently, neurological desensitization. Relaxation response can also improve negative mood states, (Benson, 1983) and escalate individuals' feelings of self-efficacy and self-control (Bandura, 1997; Everly & Lating, 2002).

Physiological techniques (Figure 6.13) constitute the following categories:

- ➢ Relaxation Therapy

- Musculoskeletal Therapy
- Imagery Technique
- Controlled Breathing
- etc

➢ Modification Strategy

- Sleeping Modification
- Nutrition Modification
- Exercise Modification
- Breathing Modification
- etc

➢ Aerobic Exercise

- Swimming
- etc

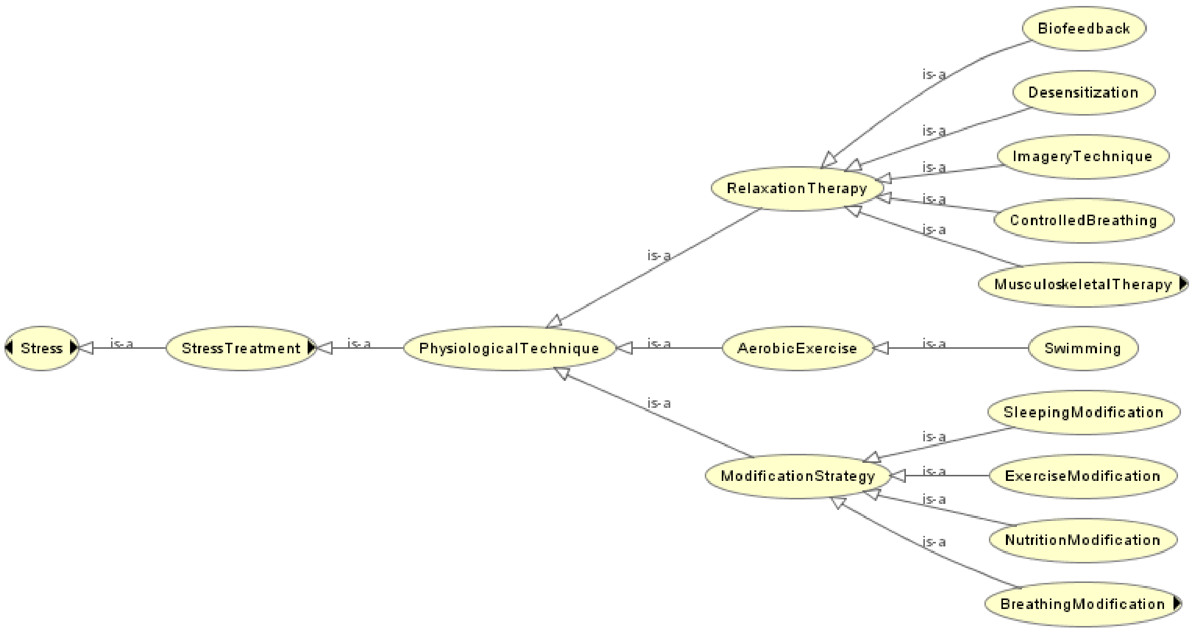

Figure 6.13. Physiological Technique

<u>6.7.4 Alternative Therapy</u>

Alternative therapies (Figure 6.14) tap into other scientifically verified and unverified techniques and strategies which people can use to overcome their feelings of anxiety and stress. These strategies may include:

- Acupressure
- Acupuncture
- Traditional Chinese Medicine
- Hydrotherapy
- Meditation
- Prayer (Benson et al., 1984)
- etc

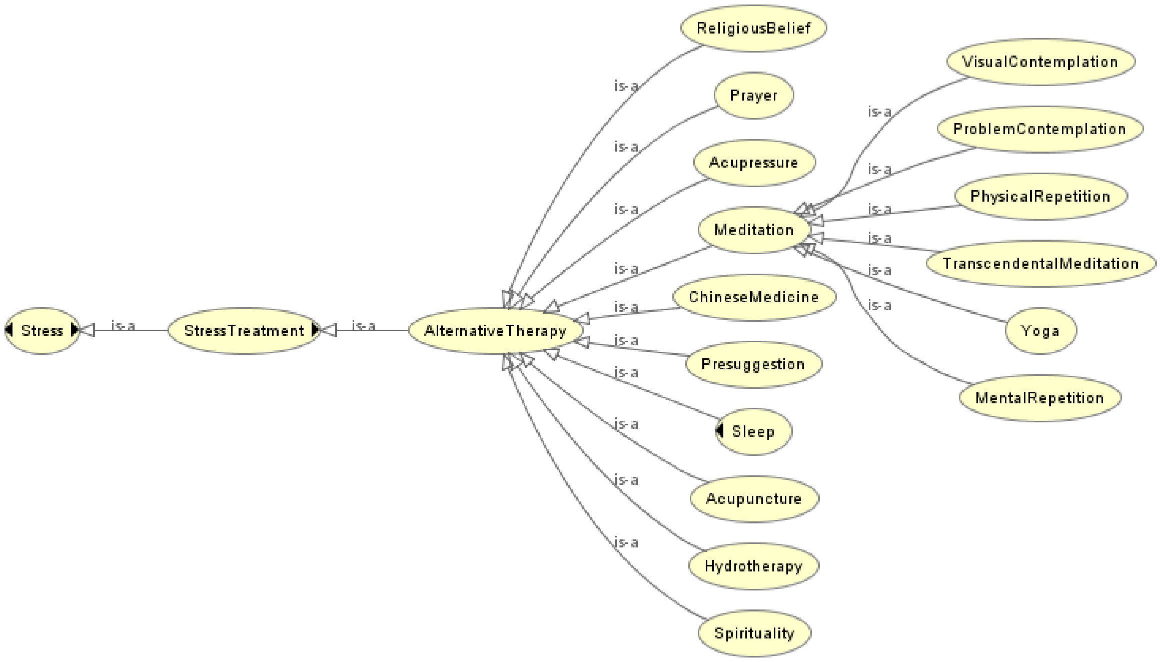

Figure 6.14. Alternative Therapy

6.8 Stress Measurement

The effective evaluation of stress and its effects on humans requires a correct specification and definition of its basic variables. Nevertheless, the ambiguity and inconsistency of definitions of stress has resulted in researchers and clinicians developing inconsistent and superfluous measurement tools to quantify different aspects of this phenomenon. Such opacity and discrepancy, in turn, have brought about a range of phenomenological and methodological divergences. For example, it has been suggested that measures of *self-report life event checklists*, that aim to evaluate the occurrence of stressful life events, also incorporate items for the assessment of stress appraisal and feelings (Monroe, 2008; Nasiri Khoozani & Hadzic, 2010).

Other commentators (Lazarus, 2006) have emphasized that an accurate evaluation of the association between stress and health initially entails having an unambiguous conceptualization and theorization of the concept of *health*. Therefore, a description of health as *social functioning* would have different ramifications for research on the correlation between stress and health than its definition as *living longer*.

The HSO has defined three general categories (Nasiri Khoozani & Hadzic, 2010) for the class of *stress measurements* to incorporate various tools devised for the evaluation of different dimensions of stress:

- Measurement of Stressor
- Measurement of Stress Feeling
- Measurement of Stress Physiology (physiological effects of stress) (Everly & Lating, 2002)

6.8.1 Measurement of Stressor

Measurements of stressors are those measurement tools which evaluate the occurrence and intensity of various stressful events in one's life. Several inventories and questionnaires have been created for this purpose.

One of the oldest measurement instruments for the evaluation of stress is the Social Readjustment Rating Scale (SRRS) (Holmes & Rahe, 1967). The original presumption held by the creators of this test was that any change (either negative or positive) exerts stressful effects on the individual as any change entails elicitation of readjustment and adaptive reactions. However, later findings demonstrated that the incidence of negative events is more detrimental to health than is the occurrence of positive life changes (Lazarus, 2006). Therefore, it was emphasized that SRRS, basically, gives an account of the occurrence of various stressors rather than correctly evaluating the individual's stress response (Everly & Lating, 2002).

Later instruments such as the Stressful Life Experiencing Screening (SLES) (Stamm, 1996; Stamm et al., 1996) aimed to measure the occurrence of adverse life events alongside the extent to which the individual has felt them to be stressful (Everly & Lating, 2002).

A more recent tool, the Life Events Scale (Wethington, 2000), offers an inclusive list of various stressful situations and incidents that presumably exert extreme and hardly adaptable demands on average individuals, resulting in psychological and physiological dysfunction and disorders. Life Events Scales is particularly suitable for a naturalistic (non-experimental) assessment of an individual's exposure to stressors (Wethington, 2000).

Following are a number of stressor measurement tools that are being represented in the HSO:

- The Stressful Life Experiencing Screening (SLES) (Stamm et al., 1996)
- The Life Stressor Checklist-Revised (Wolfe & Kimerling, 1997)
- Kidcope Checklist (Pretzilk, 1997)
- Life Events Scale (Wethington, 2000)
- Life Experience Survey (Sarason, Johnson, & Siegel, 1978)
- Measurement of Hassles
    - Almeida's Daily Inventory of Stressful Events (Almeida, Wethington, & Kessler, 2002)
    - The Hassles Scale (Lazarus, DeLongis, Folkman, & Gruen, 1985)
- Normative Event Rating (Wethington, 2000)
- Schedule of Recent Experiences (Amundson, Hart, & Holmes, 1981)
- Interview Method (e.g. Contextual Event Rating) (Wethington, 2000)

6.8.2 Measurement of Stress Feeling

It has been proposed that the evaluation of cognitive and emotional processes underlying and inducing an individual's stress feelings can be an indirect measurement of his/her stress response (Everly & Lating, 2002). Several measurement tools have been introduced to evaluate people's psychological perception and feelings of stress. For example, scales such as the *Derogatis Stress Scale* (Derogatis & DellaPietra, 1994), derived from interactional stress theory, assess individual's personality, life events, and emotional responses to stressful situations. Another example of such measures is *The Perceived Stress Scale (PSS)* (Cohen, Kamarck, & Mermelstein, 1983b) which evaluates the extent to which the person perceives an encountered event as uncontrollable or stressful. Similarly, the *World Assumption Scale* (*WAS*) (Janoff-Bulman, 1992) aims to address some fundamental assumptions people hold about their lives including the kindness and meaningfulness of the world, and their beliefs about self-worth (Everly & Lating, 2002).

The HSO has included the most-widely tools and methods for the *measurement of stress feeling* as follows:

- World Assumption Scale (WAS) (Janoff-Bulman, 1992)
- Trier Social Stress Test (TSST) (Kirschbaum, Pirke, & Hellhammer, 1993)
- Perceived Stress Scale (PSS) (Cohen et al., 1983b)
- Millon Behavioral Health Inventory (MBHI) (Millon, Green, & Meagher, 1982)
- Derogatis Stress Scale (Derogatis & DellaPietra, 1994)
- Experience Sampling Method (ESM) (Wethington, 2000)
- Retrospective Design (Wethington, 2000)
- Quasi Experimental Design (Phillips et al., 2007)
- Longitudinal Design (Phillips et al., 2007)
- Case Control Methodology (Phillips et al., 2007)

6.8.3 Measurement of Stress Physiology (physiological effects of stress)

Physiological and neurophysiological effects of stress are measured by several methods and approaches. For each, there are a number of measurement instruments (Everly & Lating, 2002). These methods may include:

- Neural Axis Measurement

- Neuroendocrine Axis Measurement
- Endocrine Axis Measurement
- Measurement of Target-Organ Effects (Everly & Lating, 2002)

6.8.3.1 Neural Axis Measurement

Tools and techniques used for measuring the neural axis activity basically evaluate the short-term and transient *state* stress responses rather than the stable *trait* ones. For example, measures identifying *aberrant evoked potentials* emerging from the sub-cortical areas of the limbic system can be used to assess current hypersensitivity of those areas. Another method appropriate for the measurement of neural axis and somatic arousal is to assess the activity of the *eccrine sweat glands* through the *electro-dermal techniques* such as *Galvanic Skin Response* (GSR). Eccrine sweat glands are predominantly located in the palms of the hand and soles of the foot and are more likely to be stimulated by psychological stressors rather than physical ones (Andreassi, 1980; Everly & Lating, 2002).

Technologies utilized for the assessment of neural axis activities include:

- Electro-Dermal Techniques
  - Galvanic Skin Response Technique
- Electromyographic Measures
- Electroencephalography
- Cardiovascular Measure
- Aberrant Evoked Potential (Everly & Lating, 2002)

6.8.3.2 Neuroendocrine Axis Measurement

The neuroendocrine axis can be examined by measuring the adrenal medullary Catecholamines (Adrenaline and Noradrenalin). Catecholamine levels can be evaluated by using samples of urine, plasma, and saliva (Everly & Lating, 2002), Chromatographic methods, or Fluorometric methods (Segerstrom & Miller, 2004).

This category of the HSO includes tools and methods such as:

- Adrenal Medullary Catecholamine Measurement
- Chromatographic Method
- Dexamethasone-Suppressed Corticotropin-Releasing Hormone Test (DEX-CRH Test) (Nieman, 2007)
- Fluorometric Method
- Radioimmunoassay Method (Segerstrom & Miller, 2004)

6.8.3.3 Endocrine Axis Measurement

According to Selye (1976b), stress response can be directly assessed through the measurement of ACTH (Adrenocorticotropic Hormone), the Corticosteroids, and the Catecholamine hormones. Therefore, the assessment of cortisol levels can be regarded as an index of ACTH activity. Many researchers believe that cortisol is an objective indicator of changes in the experience of psychological stress (Kirschbaum, Prussner, Stone, Federenko, & Gaab, 1995). The following categories are specified by the HSO as the techniques of endocrine axis measurement:

- Measurement of ACTH
- Measurement of Catecholamine
- Measurement of Corticosteroid
- Measurement of Cortisol
- CRH Challenge Test
- Cerebral Spinal Fluid Test (Everly & Lating, 2002; Gunnar & Quevedo, 2007)

6.8.4 Measurement of Target-Organ Effects

As stress can affect both physiological and psychological functions of the organism, the *measurement of target-organ effects* draws on the evaluation of various physiological and neurophysiological alterations which may occur in different organs as well as the assessment of diverse emotional, cognitive, and behavioural changes arisen in response to stress reactions (Everly & Lating, 2002). This category of the HSO incorporates two general sub-classes of *physical diagnosis* and *psychological diagnosis*, each containing several related sub-categories:

- Physical Diagnosis
  - Target Organ Pathology Assessment
  - Seriousness of Illness Rating Scale (Wyler, Masuda, & Holmes, 1968)
  - Stress Audit Questionnaire (Miller & Smith, 1982)
- Psychological Diagnosis
  - Affect Adjective Checklist (AACL) (Zuckerman, 1960)
  - Multiple Affect Adjective Checklist (MAACL) (Zuckerman & Lubm, 1965)
  - Common Grief Response Questionnaire (CGQ) (McNeil, 1995)
  - Impact of Events Scale Revised (IES-R) (Weiss & Marmar, 1997)
  - Millon Clinical Multiaxial Inventory II (MCMIII) (Millon, 1987)
  - Minnesota Multiphasic Personality Inventory (MMPI) (Hathaway & McKinley, 1940)
  - Penn Inventory for Posttraumatic Stress Disorder (PENN) (Hammarberg, 1992)
  - Profile of Mood States (POMS) (McNair, Lorr, & Droppleman, 1971)
  - Sixteen Personality Factor Questionnaire (Cattell, Cattell, & Cattell, 1993)
  - Stanford Acute Stress Reaction Questionnaire (SASRQ) (Cardeña, Classen, Koopman, & Spiegel, 1996)
  - State Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, & Lushene, 1970)
  - Subjective Stress Scale (SSS) (Bramston & Bostock, 1994)
  - Taylor Manifest Anxiety Scale (TAS) (Taylor, 1953)
  - Trier Social Stress Test (TSST) (Kirschbaum et al., 1993)
  - Ways of Coping Questionnaire (Folkman & Lazarus, 1988)

Figure 6.15 demonstrates the HSO sub-ontology of stress measurement.

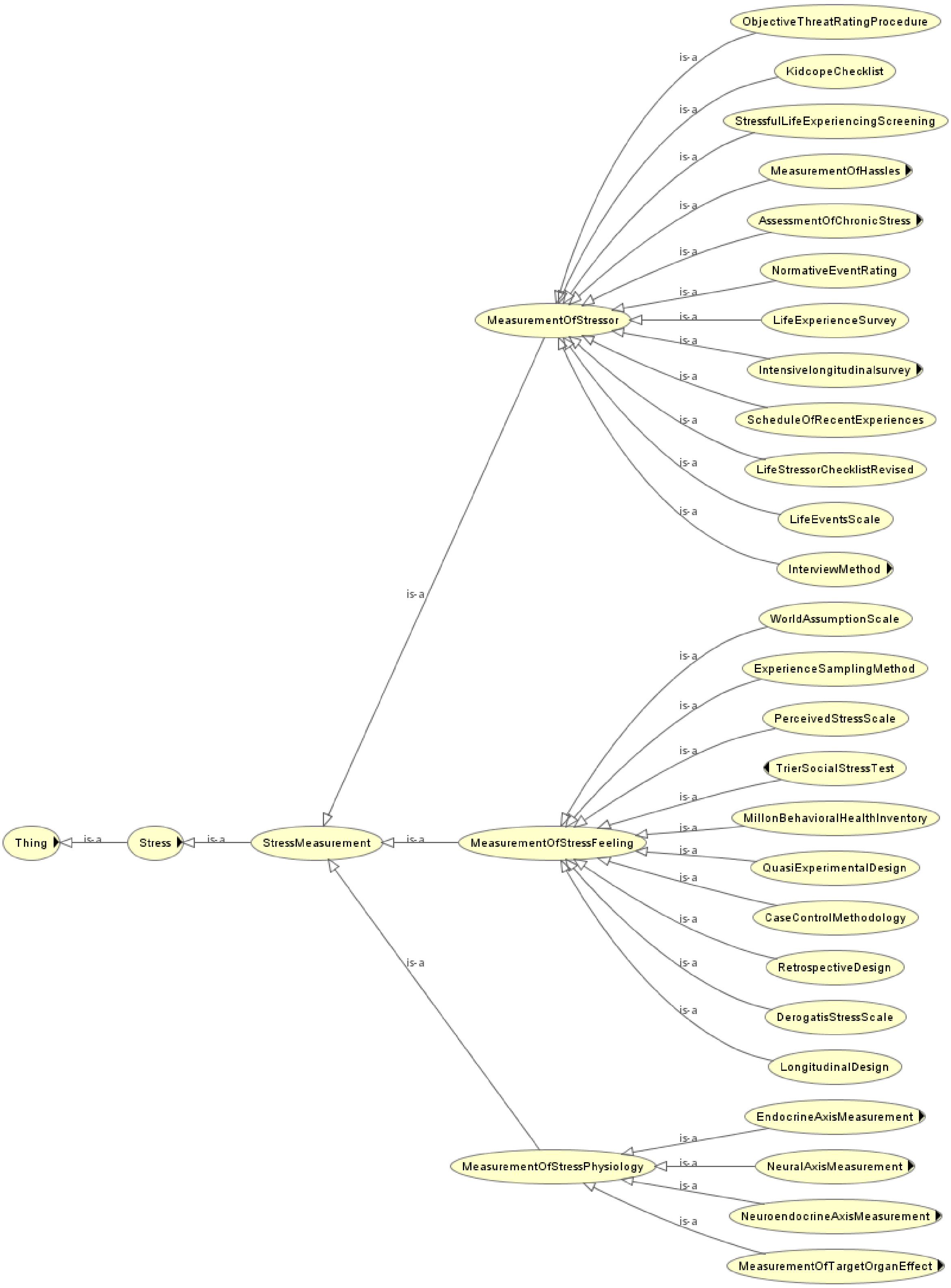

Figure 6.15. Stress Measurement

6.9 Stress Theory

The last sub-ontology of the HSO, *stress theory*, has been incorporated to cover various theories relevant to the phenomena of human stress which appear under different concepts and terms across research works.

It has been suggested that theories relating to all scientific disciplines including psychology and psychiatry rely on various types of provable or unprovable assumptions which must be subject to evaluation. To evaluate any scientific assumption, we may consider criteria such as their internal logic, reasonableness, and fecundity (Lazarus, 2006). Since the instigation of research on stress phenomena, theorists and researchers have introduced many models and theories to explain the mechanisms through which stress impacts on the organism's physiological and psychological functions. Consequently, a great deal of research works has been conducted to gather data in support of those theories. However, the criteria for preference and adoption of a certain theory over another vary depending on individuals' scientific and epistemological perspectives. For example, some critics suggest that in order for a new theory to be replaced by an old one, the new theory or metatheory must present a more successful scenario in explaining how phenomena of interest work; and that mere data cannot cause a theory to be abandoned (Kuhn, 1970; Lazarus, 2006).

The resultant numerous models and theories in fields such as human stress have made some critics (e.g. Jessor, 1996) highlight the need to consider methodological pluralism and convergence of results from multiple research methods. Jessor (1996) points to the problem of having overloading input and data without any specified destination or organization. For instance, many studies often are conducted in isolation from other relevant studies in an unsystematic way. He also mentions the problem of having *a-contextual* research and study. Accordingly, social scientists prefer to generalize their research results beyond finite contexts and specific environments to which they are applicable (Lazarus, 2006).

In response to these concerns, the HSO category of stress theory is proposed to facilitate researchers' access to various relevant theories within one framework, and increase their awareness of the potential applications (context) of a given theory. At this stage, we have included a number of well-known theories of stress as follows. Further theories and details about their explanation models are included in the HSO tool.

- Conditional Trait Approach (Wright & Mischel, 1987)
- Congruency Model (Blatt, 1974)
- Diathesis Stress Model of Depression (Monroe & Simons, 1991)
- General Adaptation Syndrome Theory (Selye, 1956)
- Idiosyncratic Personologic Style Theory (Everly, 1987)
- Kindling Sensitization Model (Post, 1992)
- Transactional Model of Stress (Lazarus & Folkman, 1984)
- Stress Vulnerability Model (Zubin & Spring, 1977)
- etc

Figure 6.16 represents the sub-ontology of stress theory. Figure 6.17 is the overall representation of the HSO and its seven sub-ontologies.

Figure 6.16. Stress Theory

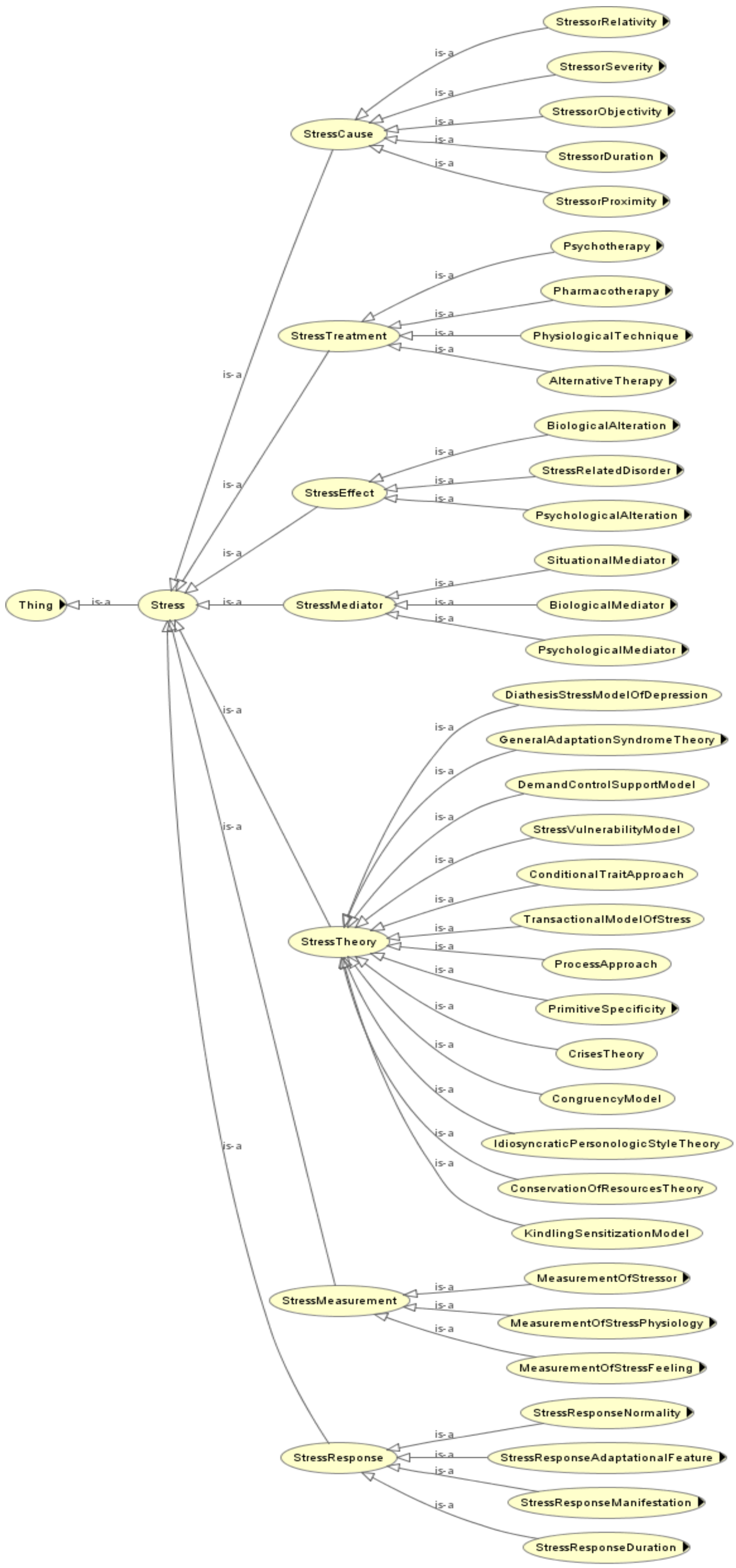

Figure 6.17. Overall Representation of the HSO

6.10 Conclusion

We presented the conceptualization of the HSO as well as an overview of stress-related literature in the domains of psychology and psychiatry. The HSO structure incorporated stress knowledge under seven categories. Our review showed that stress is influenced by and engages a wide range of psychological and physiological mechanisms which have different effects on individuals' lives. In the next chapter, the formalization of the HSO conceptualization is explained in detail.

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Chapter 7 – Formalization of the Conceptualization

7.1 Introduction

As with programming languages, the well-defined syntax of an ontology language makes the automatic processing of information possible. There are different syntax styles (e.g. XML-based RDF syntax) through which an ontology syntax can be represented. Ontology development tools are able to automatically translate the user's input data into the predefined syntax (Antoniou & van Harmelen, 2004).

Respectively, the meaning of a given domain knowledge is described precisely by the formal semantics of an ontology language. The precise formal semantics prevent the interference of various subjective interpretations in the meaning of information. In order to equip an ontology language with formal semantics, the ontology language should be mapped into a recognized logical formalism. The implemented logical formalism in OWL, the employed ontology language for the formalization of the HSO, is the description logics (Antoniou & van Harmelen, 2004).

To formalize the HSO, we used OWL as the ontology language and Protégé 4 as the ontology tool. This chapter explains how the conceptualization and classification of the previous chapter were formalized using OWL language. It also describes Protégé 4 as the ontology tool used for the formalization and visualization of the HSO. We also present a number of figures which demonstrate how Protégé 4 represents various functions of concept classification, definition, and description.

7.2. Formalization of the HSO Concepts and Relationships between Them

Concepts, individuals and the defined relationships between them have been formalized using *OWL components* of *Classes*, *Individuals*[1], and *Properties* respectively. OWL components have similarities with Protégé frame-based ontologies although they use slightly different terminology. OWL components of classes, individuals, and properties can match the components of *Classes, Instances,* and *Slots* in Protégé frames correspondingly (Horridge, 2009). In this section, we describe how the HSO concepts and relationships are represented using OWL classes and properties.

7.2.1. OWL Classes

OWL classes can be defined as *sets* or concrete representation of *concepts*. Each class contains its relevant individuals. For example, the class Catecholamine contains Adrenaline and Noradrenalin as its individuals. Overall, OWL classification is based on the subsumption (superclass-subclass) relationship (Horridge, 2009).

OWL classes are defined by use of an `owl : Class` element. In this way, we can define a class, e.g. `socialReadjustmentRatingScale` in the form of the following syntax:

```
<owl:Class
rdf:about="http://www.hso.com/ontologies/hso.owl#SocialReadjustmentRatingSc
ale">
```

[1] OWL individuals stand for objects in a universe of discourse or instances of classes. Unlike in Protégé frames, individuals in OWL are not subjected to the Unique Name Assumption (UNA), allowing the user to use two or more different names for one individual (Horridge, 2009). Since the HSO has not incorporated any individuals, we do not need to explain this notation.

```
        <rdfs:subClassOf
rdf:resource="http://www.hso.com/ontologies/hso.owl#ChecklistMeasure"/>
```

OWL language has two predefined classes. These are `owl : Thing`, the most general class containing everything; and `owl : Nothing`, which is in fact an empty class without any member. In OWL, every class can be defined as a subclass of `owl : Thing` and a superclass of `owl : Nothing` (Antoniou & van Harmelen, 2004).

7.2.2 OWL Properties

OWL properties are also equivalent to *Roles* in Description Logics, *Relations* in Object Oriented Languages such as UML, and *Attributes* in GRAIL. Properties represent the relationships between two individuals or classes. For example, the property "*increases*" can link the class Catecholamine to the class GlucoseUptake in the following way: "Catecholamine `increases` GlucoseUptake". Moreover, we can use the notion of *inverse* property to describe the above statement, i.e. "GlucoseUptake `isIncreasedBY` Catecholamine". Overall, there are three types of property: *Object property*, *Datatype property*, and *Annotation property*. Object property, such as the *increase* in the above example, associates an object to another object or a class to another class. Datatype property specifies datatype values for individuals by linking them to an rdf literal or an XML Schema Datatype such as integer, float, string, Boolean, etc. Respectively, using annotation property, we can append metadata (information such as date, creator, comment, etc) to classes, individuals, object properties, and datatype properties (Horridge, 2009).

OWL introduces two types of property elements: 1. *Objective properties*; and 2. *Datatype properties*. An objective property such as `increases` or `isMeasurementOf` links objects (entities) to other objects (entities), whereas a datatype property such as `age` or `height` connects objects to datatype values. In OWL (OWL Full) there is no predefined datatype so that the ontologist can employ XML Schema datatypes. OWL also permits the user to define *inverse properties* of properties such as `isIncreasedBy` which is the inverse property of increases. Furthermore, OWL is equipped with an owl : equivalentProperty element by use of which one can define the equivalence of a given property (e.g. declares that escalates is an equivalent property of increases) (Antoniou & van Harmelen, 2004).

7.2.3 Formal Description of the HSO Concepts

The HSO concepts or classes are described using OWL *Property Restrictions* and OWL *Boolean Combinations* (*union, intersection,* and *complement*).

7.2.3.1 OWL Property Restrictions

To describe a certain class, OWL provides the user with the facility to apply desirable restrictions such as *universal quantification* and *existential quantification* on the properties as follows:

7.2.3.1.1 Universal Quantification (owl : allValuesFrom)

The property restrictions for OWL axioms can be represented by OWL rdf : subClassOf element. This element can declare that a class *A* is a subclass of another class *A′*, concluding that every instance of *A* is also an instance of *A′*. Using this superclass-subclass expression we can also assert that class *A* (all instances of class *A*) comply with certain conditions by merely stating that class *A* is a subclass of class *A′*. In this case, *A′* is in fact the *anonymous class* of all objects that satisfy the conditions. Such anonymous classes, called *class expressions*, have no *id* and are not defined explicitly by owl : Class. They are also limited to a local scope, being used merely where the restriction applies (Antoniou & van Harmelen, 2004).

For example, a statement such as “Catecholamine is *only* secreted by Adrenal Gland”, can be represented in the following RDF superclass-subclass form to account for its universal restriction, i.e. *only*:

```
<owl:Class rdf:about="http://www.hso.com/ontologies/hso.owl#Catecholamine">
        <rdfs:label>CA</rdfs:label>
        <rdfs:subClassOf>
            <owl:Restriction>
                <owl:onProperty
rdf:resource="http://www.hso.com/ontologies/hso.owl#isSecretedBy"/>
                <owl:allValuesFrom
rdf:resource="http://www.hso.com/ontologies/hso.owl#AdrenalGland"/>
            </owl:Restriction>
        </rdfs:subClassOf>
    </owl:Class>
```

The above property restriction, `owl : allValuesFrom`, defines the anonymous class of all possible values that the property `IsSecretedBy` (`owl : onProperty`) can take. In this way, it can declare that “*only* Adrenal Gland can secrete Catecholamine”, or equivalently, all values of the property `IsSecretedBy` belong to the class Adrenal Gland. In logic, this restriction is called *universal quantification* (Antoniou & van Harmelen, 2004).

7.2.3.1.2 Existential Quantification (`Owl : someValueFrom`)

If we want to state that all instances of the class Stress Response must have at least one instance of the class Stress Mediator as their mediator, we can use the property restriction `Owl : someValueFrom` as follows:

```
  <owl:Class
rdf:about="http://www.hso.com/ontologies/hso.owl#StressResponse">
        <rdfs:subClassOf>
            <owl:Restriction>
                <owl:onProperty
rdf:resource="http://www.hso.com/ontologies/hso.owl#hasMediator"/>
                <owl:someValuesFrom
rdf:resource="http://www.hso.com/ontologies/hso.owl#StressMediator"/>
            </owl:Restriction>
        </rdfs:subClassOf>
      </owl : Class>
```

This type of restriction is called existential quantification in its logical terms (Antoniou & van Harmelen, 2004). The HSO has mostly used the existential restriction for the description of its axioms.

7.2.3.2 OWL Boolean Combinations

OWL also allows the user to use Boolean combinations of *union*, *intersection*, and *complement* to combine both `OWL : Classes` and class expressions (i.e. anonymous classes) (Antoniou & van Harmelen, 2004). For example, in the HSO, we can declare that the class `StressCause` is disjoint from the class `StressTreatment`, ensuring that no instance of the stress cause is an instance of the stress treatment and vice versa. This declaration can appear in the following syntax:

```
<owl:Class rdf:about="http://www.hso.com/ontologies/hso.owl#StressCause">
  <rdfs:subClassOf>
    <owl:Restriction>
      <owl:disjointWith
rdf:resource="http://www.hso.com/ontologies/hso.owl#StressTreatment"/>
```

```
  </owl : Restriction>
 </rdf : subClassOf>
</owl : Class>
```

The above expression states that every instance of the class `StressCause` is an instance of the complement of the class `StressTreatment`. It means that no stress cause can simultaneously be a stress treatment.

7.2.4 Definition of the Characteristics of the HSO Relationships

OWL also offers the facility to directly define and describe some characteristics for the specified property elements as to how they connect any two concepts together. Such characteristics include:

- `owl : TransitiveProperty`
- `owl : SymmetricProperty`
- `owl : FunctionalProperty`
- `owl : InverseFunctionalProperty`
- `owl : ReflexiveProperty`

With `owl : TransitiveProperty`, one can infer that if the property *P* associates object *X* to object *Y*, and also object *Y* to object *Z*, then object *X* is simultaneously associated with object *Z* via property *P*.

With `owl : SymmetricProperty`, we are able to assert that if object *X* is associated with object *Y* via property *P*, then mutually object *Y* is associated with object *X* along the same property *P*.

If we wish to declare that property *P* has at most one unique value for each individual (object), then we must use owl : FunctionalProperty. Examples of such a functional property are age or height.

Respectively, owl : InverseFunctionalProperty specifies a property along which two different individuals cannot have the same value. For example, "isDrugLabelFor" can be defined as an inverse functional property to indicate that each drug can take only one drug label.

By use of owl : ReflexiveProperty, we can declare that property *P* must associate object *X* to itself (Horridge, 2009).

The following is an example of the syntactic form of transitive property and symmetric property as appears on the object property "hasAssociationWith":

```
<owl : ObjectProperty  rdf : ID="hasAssociationWith">
    <rdf : type  rdf : resource="&owl ; TransitiveProperty" / >
    <rdf : type  rdf : resource="&owl ; SymmetricProperty" / >
    <rdf : domain  rdf : resource="#CortisolHyperSecretion" / >
    < rdf : range  rdf : resource="#DepressiveReaction" / >
</owl : ObjectProperty>
```

The above example states that CortisolHyperSecretion has association with DepressiveReaction and this association is a transitive and symmetric (two-way or mutual) one.

7.3 Representation and Visualization of the HSO using Protégé 4

Protégé 4 (Horridge, 2009) is one the latest versions of Protégé tool which stores ontologies in OWL language and employs Description Logics for its logical operations. In the following, we explain and illustrate how various features of human stress conceptualization have been represented by means of this ontology editor. Please note that we explain only those functions which have been employed in the HSO at this stage, not elaborating on the tool reasoning plug-ins.

7.3.1 Active Ontology Tab

Opening the HSO ontology on Protégé 4, we face the *Active Ontology Tab* (Figure 7.1) on which general information about the ontology is represented. As can be seen from the figure, the ontology URI (http://www.hso.com/ontologies/hso.owl) is displayed in the address bar. In the *Ontology annotations* view (on the left) we have added a general *comment* about the HSO which describes it as "*The Human Stress Ontology that conceptualizes and represents knowledge about human stress*". On the right side of the active ontology tab, the *Ontology metrics* view is presented which contains statistical information about the number of classes, properties, individuals, etc. The current version of the HSO incorporates over 2000 classes and 152 object properties.

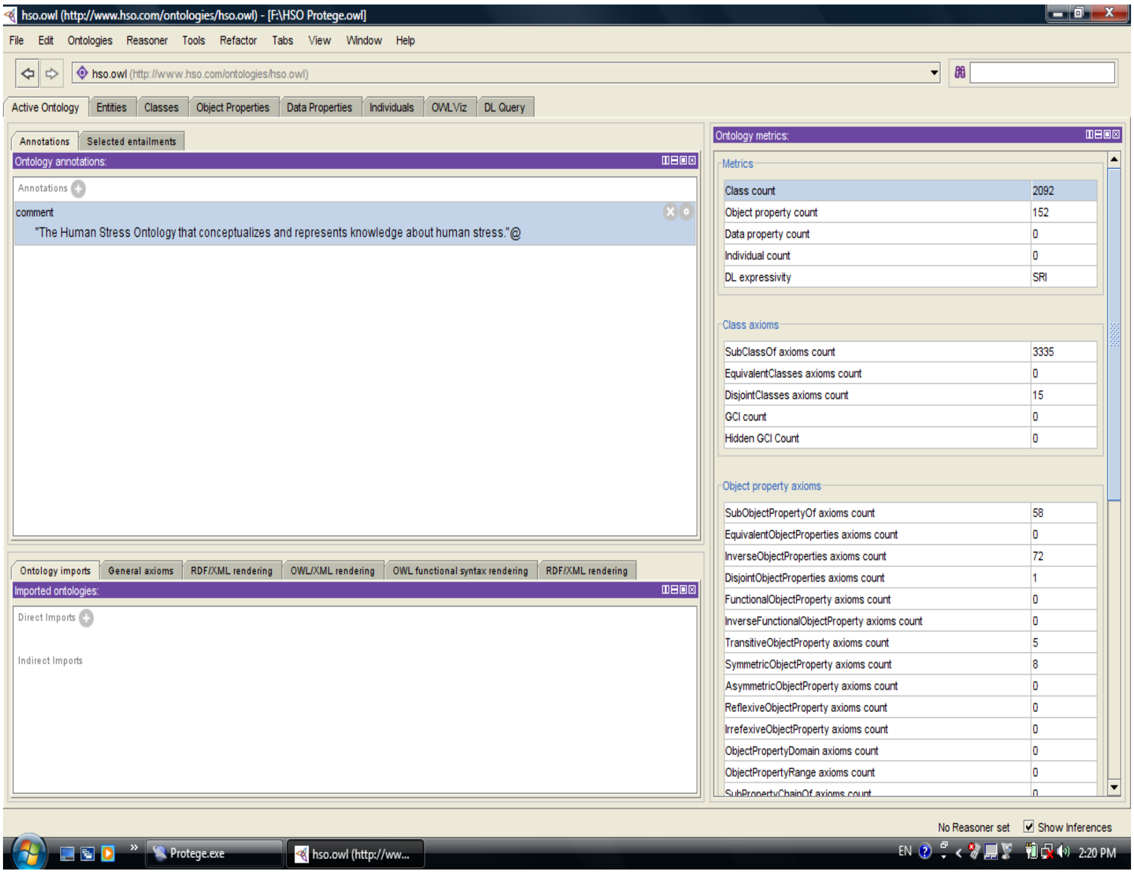

Figure 7.1. Active Ontology Tab

7.3.2 Classes Tab

By clicking on the *Classes* option of the menu we can open the *Classes Tab* on which we are able to edit the ontology classes or concepts. The class hierarchy tree is rooted from the default class `Thing`, meaning that all classes are subsumed by the class `Thing`.

On the left side of the classes tab, the *Class Hierarchy* pane can be observed. This pane provides the user with the facility to add new subclasses, add sibling classes, and delete a selected class if not desirable. The HSO has incorporated two general classes (`MeshCategory` and `Stress`) under `Thing`, each subsuming their relevant subclasses (Figure 7.2). The class MeSH Category includes those concepts from MeSH which have some associations with stress concepts, yet cannot be directly included in the class Stress. The Stress class incorporates the seven sub-ontologies of the HSO, i.e. `StressCause`, `StressMediator`, `StressResponse`, `StressEffect`, `StressMeasurement`, `StressTreatment`, and

StressTheory. By clicking on each class, their related subclasses can become visible. In OWL, the notion of subclass bears a *necessary implication*. It means that if, for example, StressRelatedDisorder is a subclass of StressEffect, then all instances of StressRelatedDisorder are also instances of StressEffect.

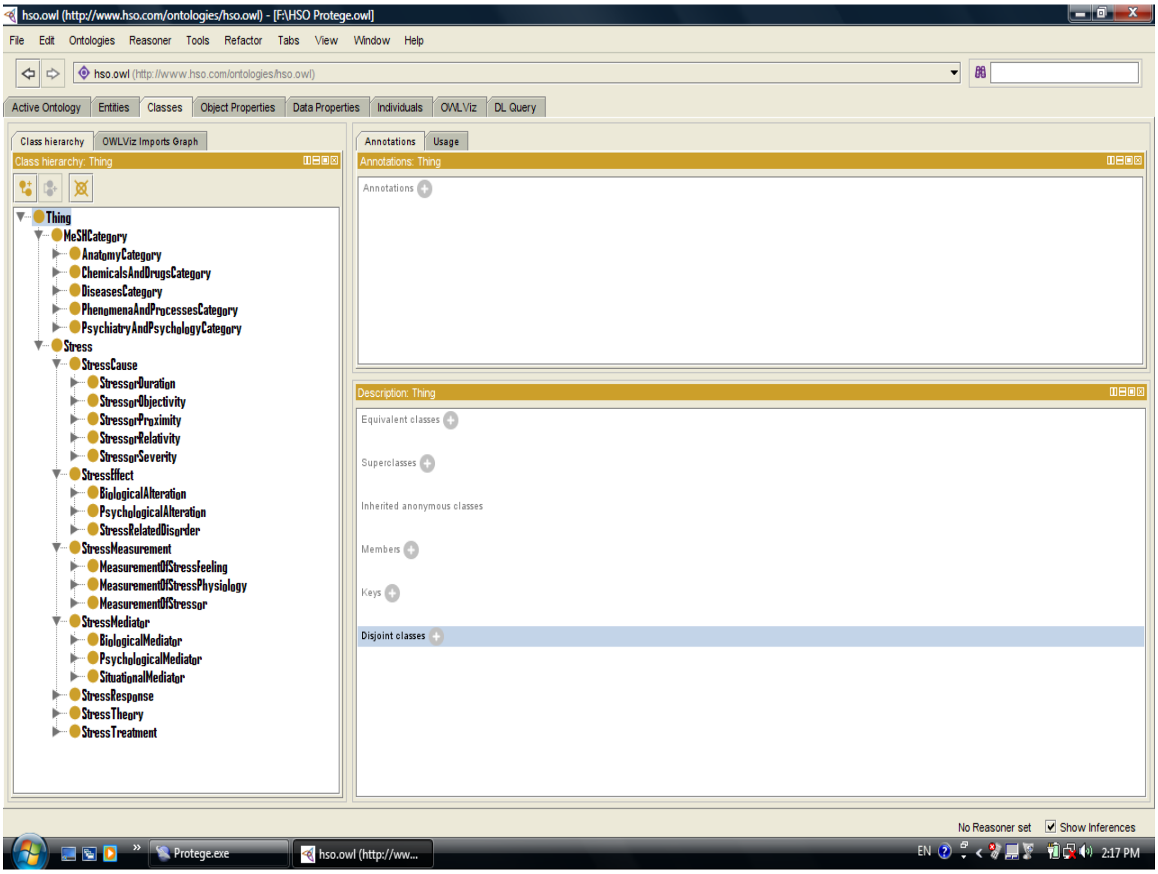

Figure 7.2. Classes Tab

7.3.3 Properties Tab

To create OWL object properties, we may use the *Object Properties Tab*. Data type properties can be included using *Data Properties Tab*. Annotation properties (metadata), however, can be added to individual, classes, and properties on most of the tabs.

Using the *Object Property Hierarchy* pane, we can create properties, sub-properties, sibling-properties, or delete a selected property if not desirable. Overall, it is recommended that properties in Protégé have the word "*has*" or the word "*is*" as a prefix. For example, the HSO axiom “DerogatisStressScale measures some PersonalityMediator” can be stated as “DerogatisStressScale isMeasurementOf some PersonalityMediator”, or inversely, “PersonalityMediator hasMeasurement some DerogatisStressScale”.

OWL property hierarchy (Figure 7.3) allows the user to specialize their properties in a desirable way. For example, the property hasAssociationWith in the HSO has taken different sub-properties of hasPositiveAssociationWith, hasNegativeAssociationWith, and isLikelyToBeAssociatedWith. This permits us to define various values for a certain relationship type between two concepts according to the evidence received from the literature or experts’ consensus. For instance, we are able to specifically express “Dementia hasPositiveAssociationWith HippocampalAtrophy”, or “EmotionalReactivity hasNegativeAssociationWith PerceivedSupport” as can be seen in Figure 7.3.

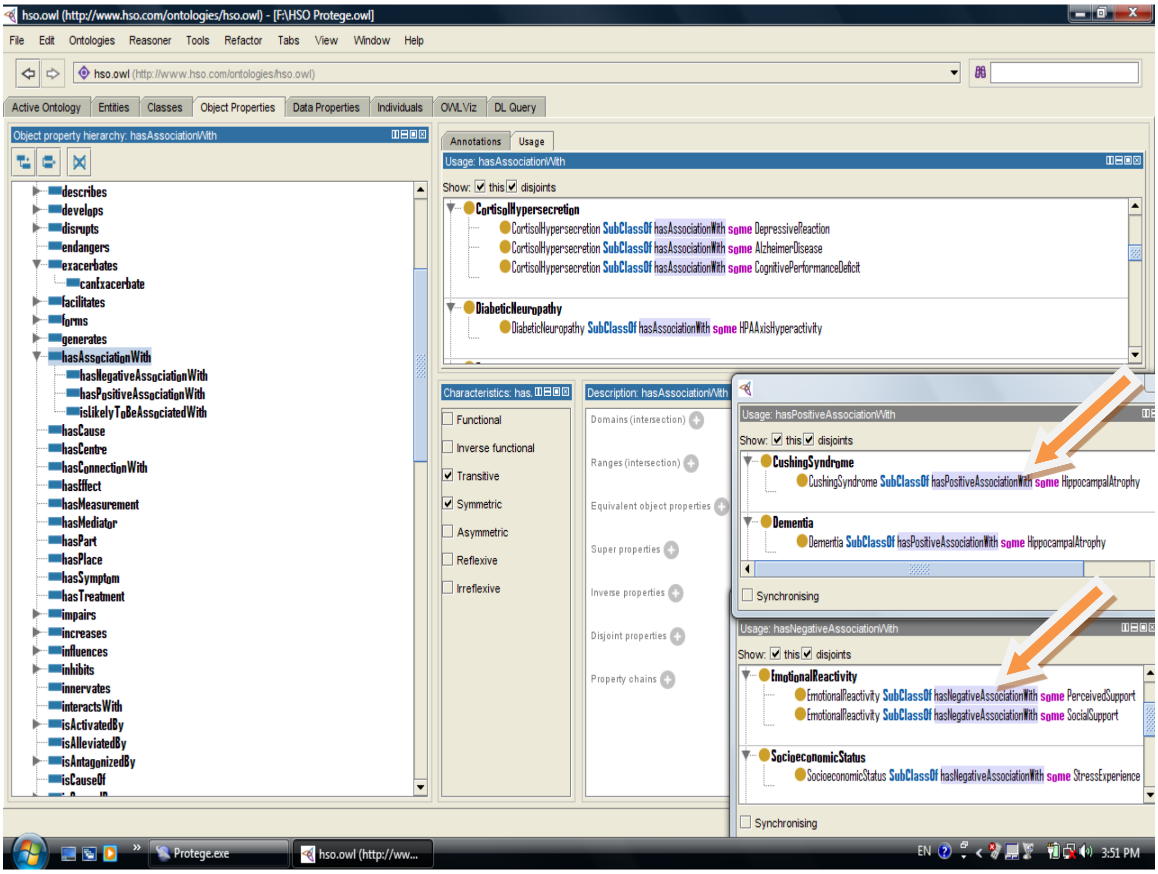

Figure. 7.3 Object Properties Tab

Protégé allows the user to define inverse properties as well as different characteristics for object properties. For example, if the object property `canIncrease` links `MetabolicStressor` to `EnergyConsumption`, then its inverse property `canBeIncreasedBy` will link `EnergyConsumption` to `MetabolicStressor`. In this way, we can infer that the inverse of the statement `MetabolicStressor canIncrease EnergyConsumption`, will be `EnergyConsumption canBeIncreasedBy MetabolicStressor` (Figure 7.4).

Each object property can further be characterised by the property characteristics which are presented in the *Characteristic View* of the object properties tab. For example, we are able to assert that the object property `hasAssociationWith` is a symmetric property, meaning that it is at the same time its own inverse property (e.g. if `HPAAxisHyperactivity hasAssociationWith StressRelatedDisorder`, then reciprocally, `StressRelatedDisorder hasAssociationWith HPAAxisHyperactivity`).

Or we may wish to define the property `canIncrease` as a transitive property to show that if, for example, `MaternalSeparation canIncrease GlucocorticoidSecretion` and `GlucocorticoidSecretion canIncrease Glycogenolysis`, then `MaternalSeparation canIncrease Glycogenolysis` inferentially.

Moreover, it is possible to disjoint one object property from another one. For example, in Figure 7.4, the object properties `canIncrease` and `canDecrease` are disjoint from each other.

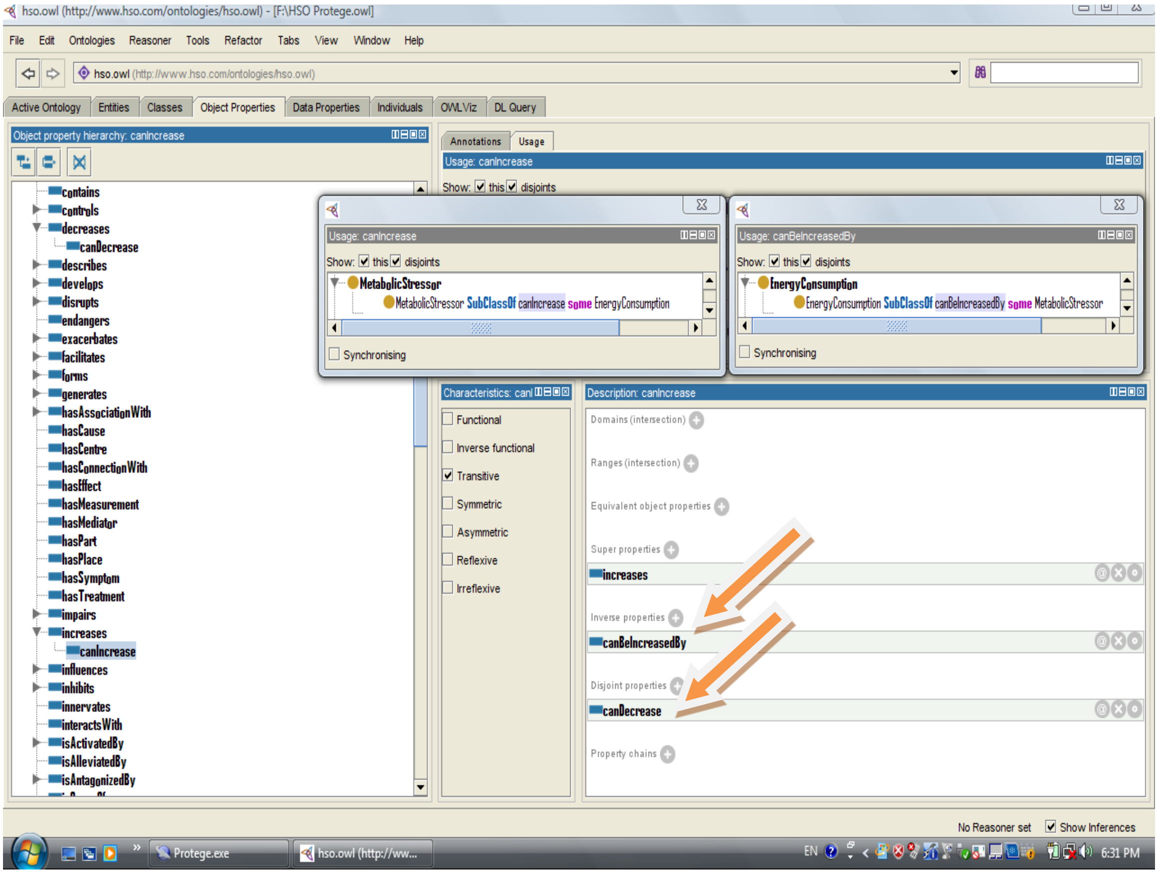

Figure 7.4. Inverse Property and Property Characteristics

7.3.4 Class Definition and Description

In OWL we can define and describe classes using *restrictions* on their properties (relationships). In this way, by assuming a restriction type as an abstract or anonymous class, we may describe a given class of individuals as a subclass of that anonymous class which complies with the restriction criteria, e.g. has at least or at most one relationship with another specified class.

Overall, there are three types of restrictions in OWL: 1) *Quantifier Restrictions* (*Existential Restrictions* and *Universal Restrictions*), 2) *Cardinality Restrictions*, and 3) `hasValue` *Restrictions*. The HSO has merely utilized the quantifier restrictions (mostly its category of existential restrictions).

Using existential restrictions, we can describe classes of individuals that have *at least one* relationship along a given property to members of another class. Existential restrictions in

Protégé 4 are denoted by the keyword "`some`". For example, the statement "`Clomipramine isTreatmentOf` **some** `ObsessiveCompulsiveDisorder`" asserts that "Clomipramine" belongs to the class of individuals that have at least one (**some**) "`isTreatmentOf`" relationship to an individual that belongs to the class "`ObsessiveCompulsiveDisorder`". Here, the restriction (i.e. `isTreatmentOf` **some** `ObsessiveCompulsiveDisorder`) can be abstracted as an anonymous class whose members are those individuals that satisfy the restriction i.e. have at least one "`isTreatmentOf`" relationship with "`ObsessiveCompulsiveDisorder`". Having assumed such anonymous classes as abstract superclasses of given class, we are able to describe that class in the OWL standard manner of superclass-subclass relationship.

Universal restrictions define classes of individuals that are associated *only* with members of another specified class along a certain property. For example, if we wish to assert that *Adrenalin* is secreted only by the *Adrenal Gland*, then we should use universal restrictions: "`Adrenaline isSecretedBy` **only** `AdrenalGland`". The HSO has rarely used this type of restriction since stress phenomena can hardly be restricted to one source.

To display or edit class descriptions in Protégé 4, we may use the *Class Description View* (Figure 7.5) which is located in the heart of the *Classes Tab*. This view provides a space for the description, display, and editing of almost all of the information about classes. As can be seen in Figure 7.5, each selected class is described in terms of its defined and anonymous superclasses under the *Superclasses* pane of the class description view.

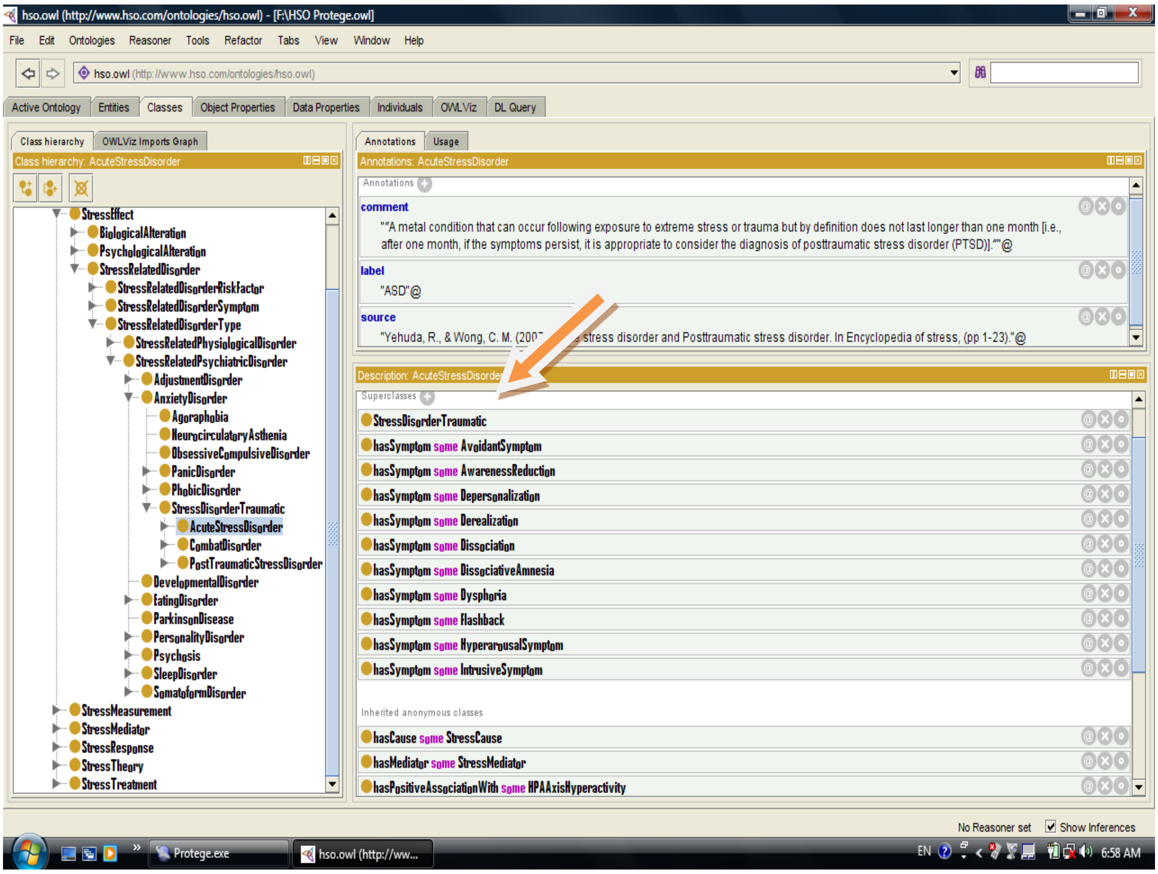

Figure 7.5. Class Description View

For example, the class "AcuteStressDisorder" has been primarily described by its direct parent (superclass), i.e. "StressRelatedDisorder", in the class hierarchy followed by its anonymous superclasses. The existential restriction "hasSymptom Some" defines the classes of individuals to which the class "AcuteStressDisorder" has at least one relationship along the property "hasSymptom". Therefore, looking at this class description, the ontology user will realize that Acute Stress Disorder is subsumed by the class Stress Related Disorders and has symptoms such as *avoidant symptom*, *awareness reduction*, *hyperarousal symptom*, *flashback*, etc.

The *Inherited Anonymous Classes* pane, just below the Superclasses pane, describes the anonymous superclasses or class conditions that the class AcuteStressDisorder has inherited from in the class hierarchy. For example, the inherited classes "hasCause some StressCause" and "hasPositiveAssociationWith some HPAAxisHyperactivity" are automatically displayed, indicating that the selected class inherits class descriptions of its grandparent superclasses "StressEffect" and "AnxietyDisorder" respectively.

The *Annotation View*, located on top of the class description view, provides the ontology creator with the facility to introduce additional information about a certain class and its descriptions. Information such as *comment*, *contributor*, *creator*, *date*, *source*, *label*, *language*, *title*, etc may inform users of various aspects of a selected concept and help them define whether a certain concept is suitable for a given application.

For instance, the HSO has employed three annotation types, i.e. comment, label, and source, for `AcuteStressDisorder`. The *comment* annotation presents the definition of the concept. *Label* represents the acronyms or alternative names which might be used for that concept. Moreover, the *source* annotation indicates where the concept or definition comes from, i.e. its *references*.

A further capability of Protégé 4 is that it allows the user to create as many annotation types as s/he wants. Taking advantage of this facility, we have created a new annotation type, called *context*, which can be used in situations where the relationship between two concepts is *conditional* and *context-dependent*. For example, in the description view of the class `PostTraumaticStressDisorder` (Figures 7.6 and 7.7) one can see that there are two apparently contradictory statements of:

1) "`PostTraumaticStressDisorder hasAssociationWith some CortisolHypersecretion`" and

2) "`PostTraumaticStressDisorder hasAssociationWith some CortisolHyposecretion`".

To avoid such contradictory statements and provide necessary information about the context in which a certain axiom applies, we have created the *context* annotations for context-dependent descriptions which can be popped open by clicking on the symbol **@** located on the right side of each class description. Using context annotations, we are able to assert that the first statement, i.e. "`PostTraumaticStressDisorder hasAssociationWith some CortisolHypersecretion`" applies in the context of *children* (Figure 7.6), but the second statement, i.e. "`PostTraumaticStressDisorder hasAssociationWith some`

CortisolHyposecretion" applies in the context of *adults* (Figure 7.7). Moreover, we are even able to add more information (annotation) to our annotations, providing greater clarity and avoiding ambiguity in concept definitions and descriptions of our ontology.

With Protégé 4 we are also able to visualize selected conceptual hierarchies in the form of a graph. Figure 7.8 is an example of OWL visualized graph for the class of AntidepressantType and its subclasses. OWL graph represents *taxonomy* relationships between the concepts.

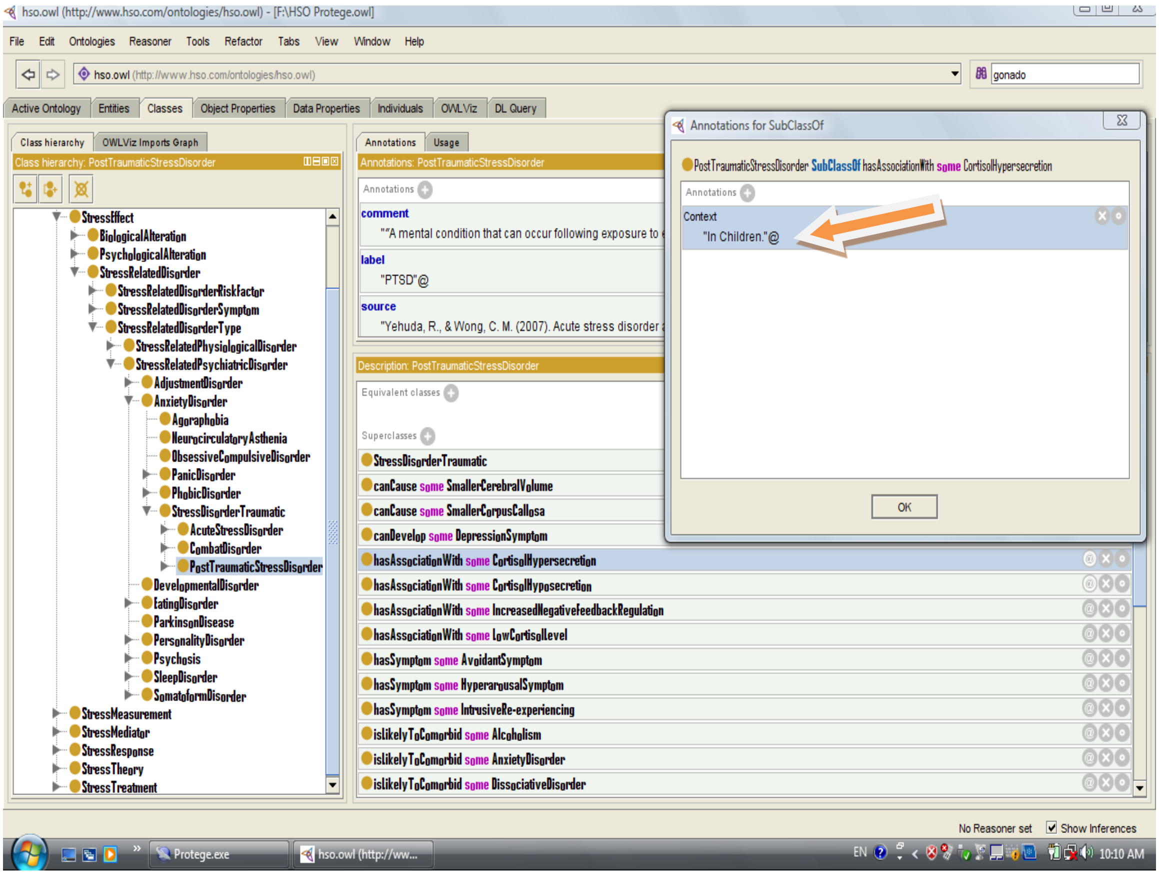

Figure 7.6. Context Annotation (Context: In Children)

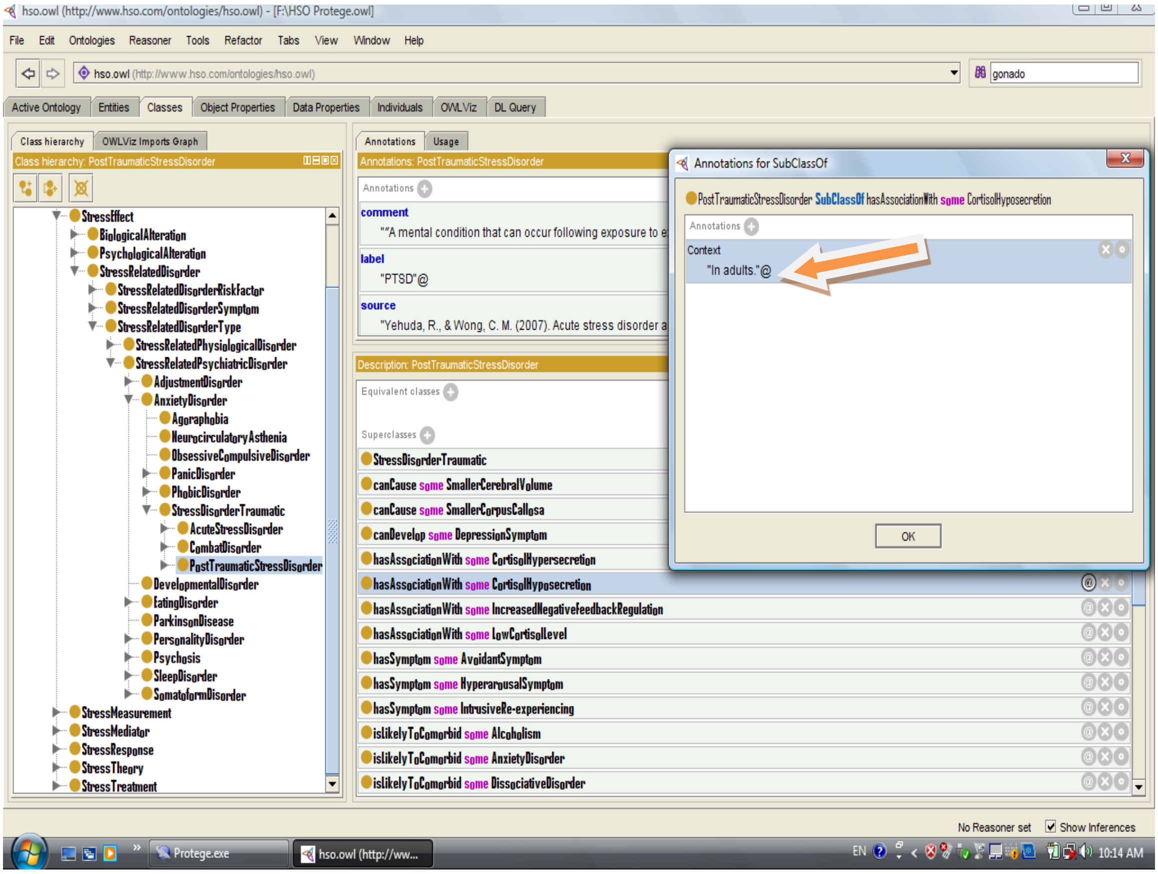

Figure 7.7. Context Annotation (Context: In Adults)

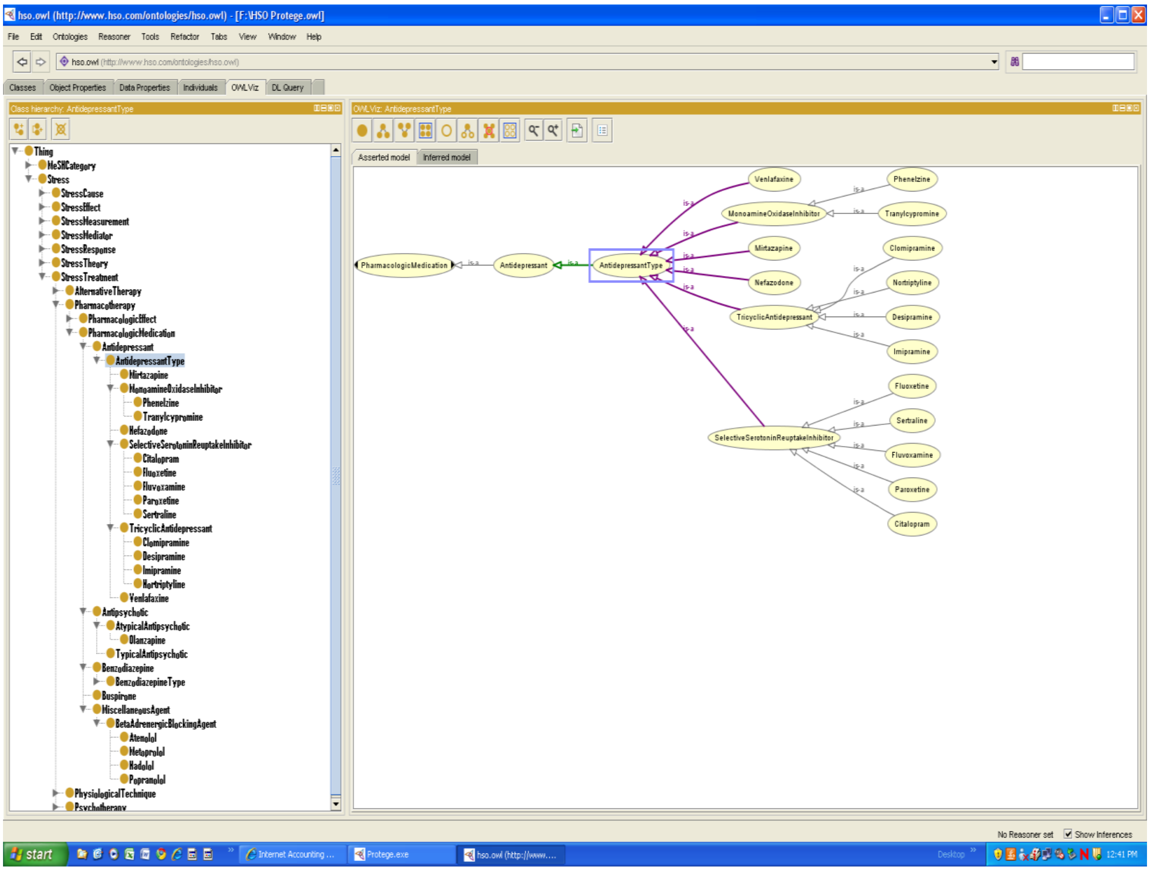

Figure 7.8. Visualized Graph of the Class `AntidepressantType`

The described HSO tool can provide researchers and clinicians with a structured and linked framework of concepts and their relationships which is easy to use, browse, and manipulate. For example, clinicians can have access to information about different pharmacologic medications available for a certain stress-related disorder and obtain relevant information regarding their commercial labels, effects, side-effects, and various relationships they may have with other physiological and psychological functions. Figure 7.9 illustrates this functionality of the HSO.

The class hierarchy view in Figure 7.9, has listed a wide-ranging taxonomy of *pharmacologic medications* for stress-related disorders. Using this taxonomy, the clinician can easily recognize that, for instance, `Benzodiazepine` is subsumed by `PharmacologicMedication`, has label `BZD`, subsumes medications such as `Alprazolam`, `Chlordiazepoxide`, `Clorazepate`, etc, and has the following class descriptions:

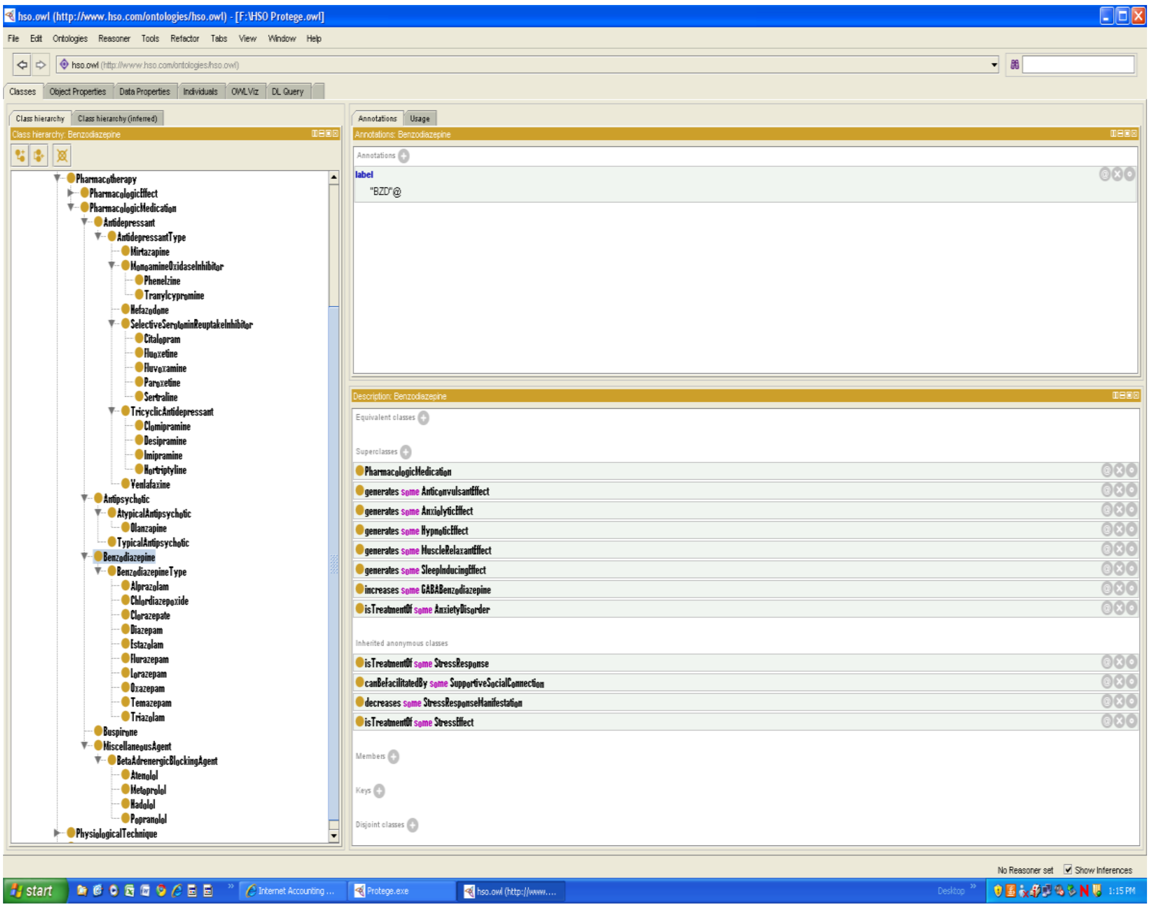

Figure 7.9. The Class Hierarchy of `PharmacologicMedication` and Description View of `Benzodiazepine`

1) `generates some AnticonvulsantEffect`

2) `generates some AnxiolyticEffect`

3) `generates some HypnoticEffect`

4) `generates some MuscleRelaxantEffect`

5) `generates some SleepInducingEffect`

6) `increases some GABABenzodiazepine`

7) `isTreatmentOf some AnxietyDisorder`

8) `isTreatmentOf some StressResponse`

9) `canBeFacilitatedBy some SupportiveSocialConnection`, and

10) `isTreatmentOf some StressEffect`

7.4 Conclusion

This chapter described how the conceptualization of the HSO was represented and formalized using OWL ontology language. We explained how ontology classes can be described and constraints can be applied using different features and components of OWL language. We also described the representation and visualization of the HSO in Protégé 4 as our chosen ontology tool. This tool allowed us to define and describe stress-related concepts using OWL language. By using different tabs and views provided by Protégé 4, we were able to create detailed and explicit illustrations of our knowledge description of human stress. Furthermore, we showed how researchers and clinicians can have access to, browse, and manipulate their clinical data via the structured and linked framework of concepts and their relationships using the HSO tool. In the next chapter, we elaborate on the proposed methodology for the refinement and evolution of ontology relationships based on scientific evidence.

References

Antoniou, G., & van Harmelen, F. (2004). Web Ontology Language: OWL In S. Staab & R. Studer (Eds.), *Handbook on ontologies* (pp. 67-92). Berlin Heidelberg: Springer.

Horridge, M. (2009). A practical guide to building OWL ontologies using prot´eg´e 4 and CO-ODE tools (1.2ed.).

Chapter 8 –Development of a Methodology for the Evolution of Ontology Relationships

8.1 Introduction

In addition to experts' consensus, it is desirable to define ontological relations between any two concepts in a scientific ontology based on scientific evidence in order to give an accurate and reality-based account of the ontological statements. In addition, it is important to accomplish this task in an automatic manner to reduce the current labour and time spent on the manual refinement of ontology relationships.

One of the ways to address this issue is to relate ontological relations to different research results obtained from various studies. To achieve this, we proposed an Evidence-Based Evolving Ontology (EBEO)[1] methodology which can model and represent the level of relationship between any two given concepts in the Domain Ontology (DO). The EBEO methodology implements a Systematic Review Ontology (SRO) and a Fuzzy Inference System (FIS), embedded in an Automated Systematic Review Agent (ASRA), to refine the ontological relationships of the DO. The FIS can model the partial level of truth between two given concepts.

In order to find out the degree of evidentiality of a theory, which has been addressed by a wide range of studies, researchers have to undertake extensive Web searches, paper reviews, and statistical analysis. Furthermore, they are expected to keep track of the emerging study results to keep up to date with any supporting evidence or refutation of a scientific hypothesis in their domain of study. The EBEO methodology can potentially streamline this process, assisting researchers to keep pace with the latest research results about various degrees of proof or refutation of a scientific theory in the form of explicit facts which are represented in

[1] The proposed methodology is part of the Evidence-Based Evolving Ontology (EDBEO), an ontology evolution methodology which was described in Nasiri Khoozani, Hussain, Dillon, and Hadzic (2010). For the purpose of this thesis, we did not include the Discovery element of the original work.

the domain ontology. Additionally, by retrieval, analysis, and representation of the results of the latest research works, it has the potential to produce a state-of-the-art report to investigators, thereby allowing them to write more inclusive and accurate review papers.

This chapter outlines the solution we proposed for the refinement and evolution of ontology relationships between concepts in the HSO.

8.2 Components of the Evidence-Based Evolving Ontology (EBEO)

To refine and evolve ontology relationships based on the evidence obtained from scientific works, we proposed an ontology evolution methodology, EBEO, which incorporates the following three components:

1. Domain Ontology (DO)
2. Systematic Review Ontology (SRO)
3. Automated Systematic Review Agent (ASRA)

8.2.1 Domain Ontology (DO)

The DO is the ontology, e.g. the HSO, for whose concepts we intend to define evolving evidence-based relationships. For example, we may intend to define, refine, and evolve the relationship "*stimulates*" between the two HSO concepts "Stress Reaction" and "Cortical Secretion" based on the receiving evidence from relevant literature.

8.2.2 Systematic Review Ontology (SRO)

The SRO is a higher-level ontology which is used for the annotation of theoretical statements by analysing the scientific articles. This ontology can be comparable to the *scientific research ontology* (De Almeida Biolchini, Mian, Natali, Conte, & Travassos, 2007) which was described in Chapter 1.

Design of the SRO is guided by the concepts and relationships in the DO, extracted knowledge from scientific research ontologies and other related databases and controlled vocabularies.

SRO incorporates those terms (e.g. verbs) emerging in the scientific literatures which point to the relationships between two concepts as to their description of research outcomes. The SRO repository incorporates a rich terminology of specific nouns and phrases which appear in the theoretical statements (in the form of concepts and their relationships) across scientific article conclusions or abstracts[2] .

For example, to encompass sufficient terminology for the mapping of a theoretical statement such as "Stress Response *reduces* Gonadotropin Secretion", the SRO repository incorporates a rich amalgamation of specific nouns and phrases such as "Stress Response", and "Gonadotropin Secretion" as well as specific verbs (or relationships) such as "*reduce".* Here, the specific nouns, phrases, and verbs correspond to the specialized concepts and represent the operational relationships between them for which proof the researcher has reported his/her results. Moreover, each concept (noun or verb) in the SRO is recorded accompanied by it synonyms, hyponyms or different spellings. For instance, there are various labels and synonyms of *"decrease", "diminish",* or *"lessen"* for the verb *"reduce"* in order to capture different terminologies used by researchers to verbalize their theoretical statements. Specification and definition of a concept and its labels can be guided by linguistic knowledge and critical thinking instructions.

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[2] The results of research works published in scientific domains often include statements about the proof or disproof of a relation between two concepts which are usually contained in abstract or conclusion sections of articles.

8.2.3 Automated Systematic Review Agent (ASRA)

To determine and evolve the relationship between any two concepts in the DO, we propose to develop an ASRA. The ASRA is an agent that incorporates a FIS and a SRO in order to automatically refine ontological relationships between any two given concepts in the DO. Unlike the work of De Almeida Biolchini et al. (2007) (Chapter 1) which utilized ontology as a facilitating tool for systematic review, the ASRA employs the voting method of systematic review as a strategy for the refinement of ontology relationships. In the next sections, we explain the characteristics of the FIS and its functionality in the ASRA for updating the relationships between ontology concepts.

8.2.4 Fuzzy Inference System (FIS)

Fuzzy Inference System (FIS) (Passino & Yurkovich, 1998) is a computer model grounded in *Fuzzy Set Theory*[3] and *Fuzzy Logic*[4] (Zadeh, 1975) (Jang, Sun, & Mizutani, 1997) which is utilized to define and represent changes of linguistic values in an automatic and consistent manner.

Fuzzy logic is capable of reasoning with and modelling the vagueness of natural language statements about fuzzy phenomena which lack crisp, finite and distinctive boundaries in the experience of daily life. In this way, one is able to create a more accurate and reliable

[3] Since the classical set theory was incapable of assigning the degrees of memberships to the elements in a given set, fuzzy set theory (Zadeh, 1965) was proposed as a strategy for the gradual evaluation of the membership of elements in a set. To achieve this, fuzzy set theory implements the notion of membership function which is valued in the unit interval [0, 1]. The fuzzy set theory has proved effective in domains where experts deal with incomplete or imprecise information such as the field of bioinformatics (Berkan & Trubatch, 1997; Torres & Nieto, 2006).

[4] Fuzzy logic (Zadeh, 1972) is a type of multi-valued logic which is based on fuzzy set theory and aims to perform approximate, rather than exact, reasoning. Contrary to the classical binary (crisp) logic, fuzzy logic uses fuzzy variables with various truth values ranging between 0 and 1.

mathematical representation of the *partial truth* and *uncertainty* of the fuzzy data. For example, it can be considered as an effective strategy for dealing with and representing infinite values such as "*extremely*" or "*approximately*" to which computation the conventional two-valued (0 and 1) Boolean logic cannot be applied (Passino & Yurkovich, 1998).

Figure 8.1 represents a schematic view of the EBEO methodology. As can be seen from the figure, the EBEO methodology first implements a SRO to retrieve evidence from the scientific literature. The received evidence, then, will be processed by the FIS, embedded in the ASRA, to refine a given ontology relationship between the two concepts in the DO. Based on the FIS analysis, the relationship between any two concepts is updated accordingly. In the next section, we elaborate on this process.

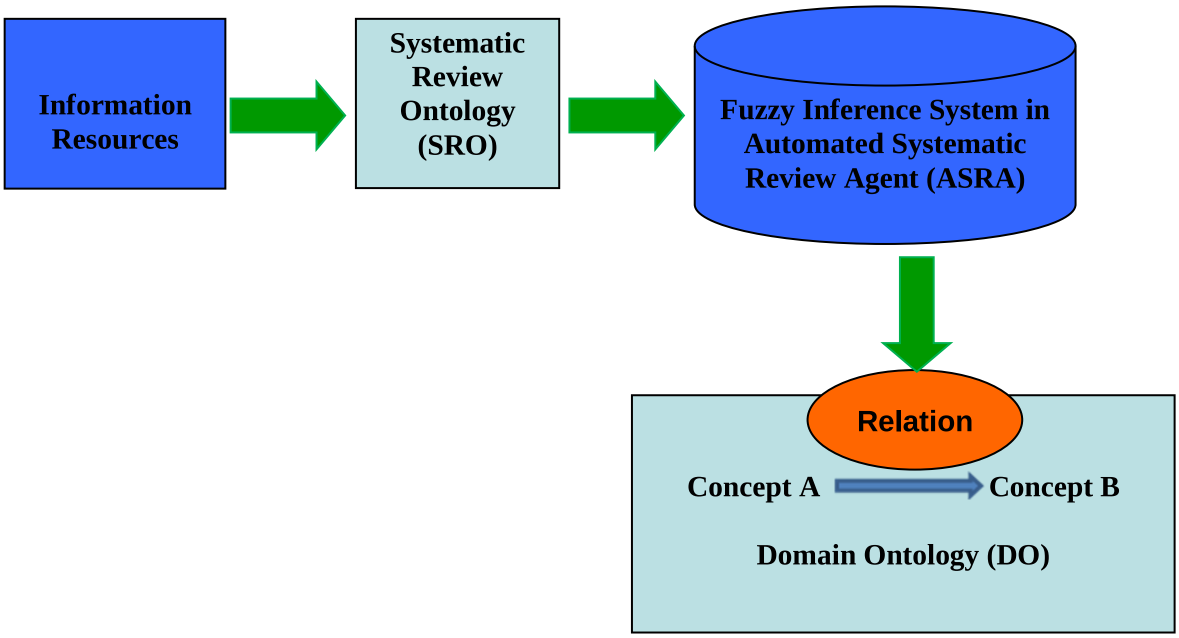

Figure 8.1. A schematic representation of the EBEO methodology

8.3 The Process of Evidence-Based Evolving Ontology (EBEO)

The following is a description of the different phases of our approach:

8.3.1 Annotation and Retrieval of Theoretical Statements from Scientific Databases

In the first step, the higher-level ontology (SRO) is designed. In the next stage, using the SRO terminology, the ASRA implements annotation tools to select relevant articles which contain identifiable theoretical statements (e.g. expressions in the form of: *X influences Y*) as to the corroboration or disproof of relationships between two concepts. Such theoretical statements are then identified, retrieved, and imported into a separate database. These extracted theories, in the next step, are used by the ASRA to refine the corresponding ontological relationships between concepts of the domain ontology (DO).

8.3.2 Calculation of the Type and Percentage of Different Relationships

This phase is a two-step process. In the first step, the type of article conclusion is determined. In the second step, the level of each type of conclusion is computed.

Using the election mode (voting method) of a simple synthesis systematic review, ASRA coalesces all extracted theoretical statements which point to negative, positive, or neutral relations between two concepts, and then performs a statistical analysis in order to work out the percentage of each type of relationship in terms of the corroboration or refutation of a given theory.

For example, the results of a voting calculation may show that among 100 selected research works, 60 studies report the existence of a positive association between two variables, 20 studies obtained negative associations, and the rest of 20 demonstrated no significant correlation (De Almeida Biolchini et al., 2007).

8.3.3 Modification of the Ontology Relationships in the Domain Ontology

The evidence obtained from the SRO can be corresponded with the modification of the relations in the DO in an automated way such that the more evidence (i.e. higher percentage of positive associations) is obtained from the SRO, the more a relevant ontology relation in the DO will alter toward a positive indication. For example, the more corroborating evidence is received about the existence of a positive relation (e.g. *increase*) between two concepts (e.g. Stress Response and Gonadotropin Secretion), the stronger (more proving or affirmative) the ontology relationship between those concepts becomes in the DO. Using this strategy, upon the receipt of a significant percentage of verifying evidence from the SRO, the existing "*is likely to increase*" relationship between two DO concepts (e.g. Stress Response *is likely to increase* Gonadotropin Secretion) would become "*is highly likely to increase*" relationship (i.e. Stress Response *is highly likely to increase* Gonadotropin Secretion). One practical strategy we can use to modulate these ontology relationships is to identify them as fuzzy variables having various linguistic values.

8.3.4 Justification of the Use of Fuzzy Inference System for the Evolution and Update of Ontology Relationships

Given the increasing mass of information in the scientific literature, it is better to have an automated tool that is able to analyse the information stored in the databases and, based on the results of that analysis, determine the level of relationship between any two ontological concepts in the DO. Therefore, FIS was utilized as an effective automated tool for the implementation of this strategy.

FIS considers ontology relationships as fuzzy variables which can be modified by being assigned various linguistic values. For example, "*increases*" can take different linguistic values of "*is likely to*", "*is highly likely to*", "*is less likely to*", "*does not*", etc according to the percentage of verifying evidence being stored and accrued in the SRO.

In this fashion, an existing ontology relationship such as "*is less likely to increase*" can keep taking more confirmative values (e.g. "*is likely to increase*" → "*is highly likely to increase*" → "*does increase*") as it receives more weight (proving evidence) from the ASRA. Conversely, the incoming disproving research conclusions can continuously dwindle the value of "*is less likely to increase*" until it gets to the "*does not increase*" point.

8.3.5 Stages of the Fuzzy Inference System

The FIS go through different stages to perform their tasks. These include: fuzzification of input data, application of fuzzy rules, and defuzzification of the output.

8.3.5.1 Identification and Fuzzification of the Input Data

In the fuzzification stage, crisp values of the linguistic variables are transformed into grades of membership to form the input of our fuzzy rules. The input (antecedent) data for each theoretical statement constitutes two parts:

1. *Type of Research Results* (*TRR*), and
2. *Level of Proof* (*LOP*)

Figure 8.2 represents an overview of the proposed fuzzy model in the EBEO approach. As can be seen from the figure, the FIS takes the TRR and LOP as its input variables and, based on this, modify the ontological relationships as its output variables.

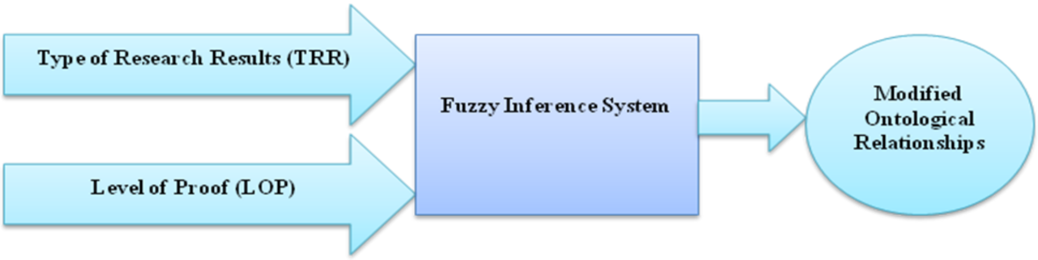

Figure 8.2. Overview of the fuzzy inference system for the modification of ontological relationships

In the following we elaborate on each input variable.

1. Type of Research Results

Type of Research Results (TRR) indicates the type of theoretical statements, in terms of their proving, disproving, or neutral states, which have been stored in the SRO database. For example, statements such as "*stress response increased Gonadotropin secretion*", "*stress response decreased Gonadotropin secretion*" or "*stress response had no significant association with Gonadotropin secretion*" point to different types of research results (positive, negative, and neutral correspondingly).

All such statements are reduced by the system into five general categories of:

- *high positive conclusion (+veH)*
- *positive conclusion (+ve)*
- *neutral conclusion* (*NEU*)
- *negative conclusion* (*–ve*), and
- *high negative conclusion* (*–veH*)

Hence, a high positive conclusion represents the likelihood of a strong proving relationship between the two concepts. A positive conclusion type represents the likelihood of a moderate proving relationship being present between the two concepts. The neutral conclusion is used to represent the likelihood of no significant relationship existing between the two concepts;

whereas, a negative conclusion type stands for the likelihood of a normal disproving relationship being present between them. A high negative conclusion indicates the likelihood of a strong disproving relationship between the two concepts. The membership function of the TRR, as illustrated in Figure 8.3, is defined as:

μ *+veH* (TRR) = 0 (if $0 < x < 1$)

$\frac{1.2 - x}{0.2}$ (if $1<x<1.2$)

1 (if $1.2 < x < 2$)

μ *+ve* (TRR) = 1 (if $0 < x < 1$);

$\frac{x - 1}{0.2}$ (if $1 < x < 1.2$);

0 (if $1.2 < x < 2$)

μ *NEU* (TRR) = 0 (if $-2 < x <-0.1$)

1 (if $x = 0$)

0 (if $0.1 < x < 2$)

μ *–ve* (TRR) = 1 (if $0 < x < -1$);

$\frac{-1.2 - (x)}{-0.2}$ (if $-1 < x < -1.2$);

0 (if $-1.2 < x < -2$)

1

μ *–ve H* (TRR) = 1 (if $-2 < x < -1.2$);

0 (if $0 < x < -1$)

$\frac{-1.2 - (x)}{-0.2}$ (if $-1 < x < -1.2$)

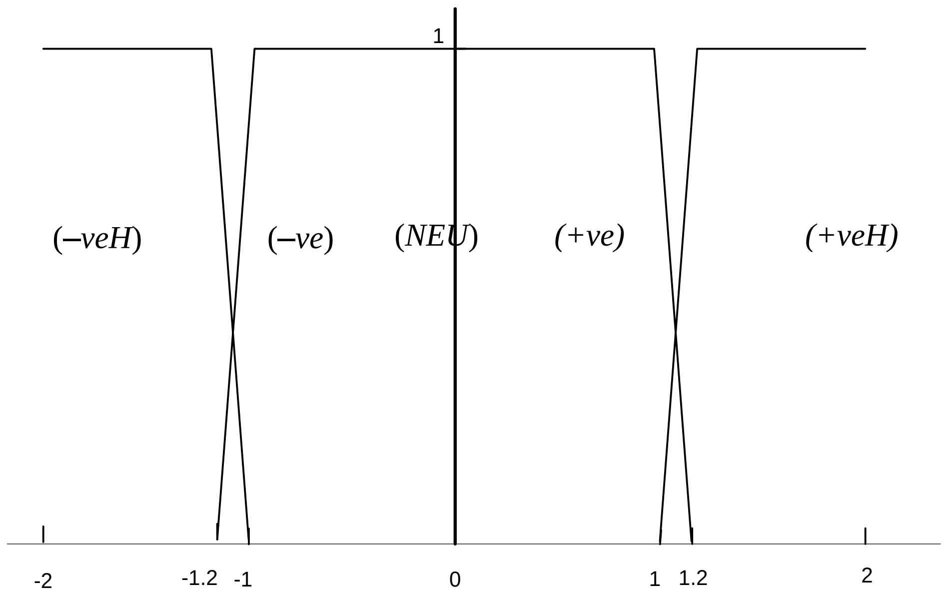

Figure 8.3. The membership function representing the five different Types of Research Results. The X axis represents the TRR; the Y axis represents the Degree of Membership (DOM).

2. Level of Proof (LOP)

The second component of the input indicates the level of severity of the TRR (Type of Research Results) which demonstrates the Level of Proof (LOP) obtained from the considered articles. The LOP is represented using a trapezoidal function which has three fuzzy sets: Low (L), Medium (M) and High (H). The membership function of the LOP, as is represented in Figure 8.4, is defined as:

μ_{Low} (LOP) = 1 (if 0 < x < 20); $\frac{30-x}{10}$ (if 20 < x < 30); 0 (if 30 < x < 100)

μ_{Medium} (LOP) = 0 (if 0 < x < 20); $\frac{x-20}{10}$ (if 20 < x < 30); 1 (if 30 < x < 55); $\frac{70-x}{15}$ (if 55 < x < 70); 0 (if 70 < x < 100)

μ_{High} (LOP) = 0 (if 0 < x < 55); $\frac{x-55}{15}$ (if 55 < x < 70); 1 (if 70 < x < 100)

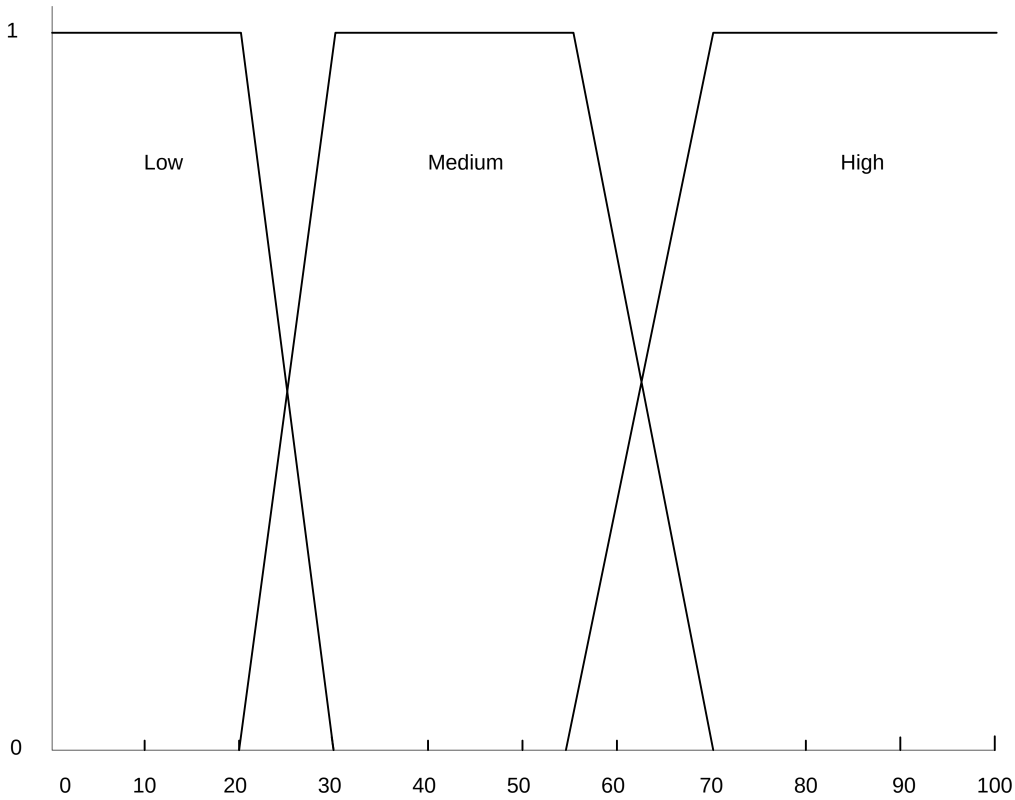

Figure 8.4. The membership function representing the three different degrees (low, medium, high) of the Level of Proof (LOP). The X axis represents the LOP; the Y axis represents the DOM.

8.3.5.2 Definition and Application of the Fuzzy Rules

In the second stage, fuzzy rules are defined and applied. Fuzzy rules are conditional statements which appear in the form of "*IF x is A: THEN y is B*". The first part of the fuzzy rule (i.e. *IF x is A*) is termed the *antecedent* (*input* in the previous section). Correspondingly, the second part of the fuzzy rule (i.e. *THEN y is B*) is denoted as the *consequent*. In the last phase, i.e. defuzzification stage, the fuzzy outcomes of each variable will be turned into a single number which is quantifiable for decision making purposes. To explain this process, we use our earlier example (*stress response increases Gonadotropin secretion*).

The antecedent (input) component of the fuzzy rules for each theoretical statement constitutes two parts of the TRR and LOP as described in the previous section.

The output (consequent) of the fuzzy rules is one of the six linguistic values of: *does not*, *is highly unlikely to*, *is unlikely to*, *is likely to*, *is highly likely to*, and *does*. Depending on the values of the TRR and LOP of the input, the ontology relation variable (e.g. *increases*) takes one of these output linguistic values. The fuzzy rules are represented in Table 8.1:

Fuzzy Rules		**TRR**		**LOP**		**Output**
Rule 1	If	+*veH*	And	*H*	Then	*does*
Rule 2	If	+*veH*	And	*M*	Then	*does*
Rule 3	If	+*veH*	And	*L*	Then	*is likely to*
Rule 4	If	+*ve*	And	*H*	Then	*is highly likely to*
Rule 5	If	+*ve*	And	*M*	Then	*is likely to*
Rule 6	If	+*ve*	And	*L*	Then	*is unlikely to*
Rule 7	If	*NEU*	And	*H*	Then	*is highly unlikely to*
Rule 8	If	*NEU*	And	*M*	Then	*is highly unlikely to*
Rule 9	If	*NEU*	And	*L*	Then	*is unlikely to*
Rule 10	If	(–*ve*)	And	*H*	Then	*is unlikely to*
Rule 11	If	(–*ve*)	And	*M*	Then	*is unlikely to*
Rule 12	If	(–*ve*)	And	*L*	Then	*is unlikely to*
Rule 13	If	(–*veH*)	And	*H*	Then	*does not*
Rule 14	If	(–*veH*)	And	*M*	Then	*does not*
Rule 15	If	(–*veH*)	And	*L*	Then	*is unlikely to*

Table 8.1. Fuzzy rules for determining the relationship between any two concepts

8.3.5.3 Defuzzification of the Output Results

In the defuzzification stage, the fuzzy quantification of each variable will be turned into a single number which is then mapped to the ontology relationships in the DO in order to determine the level of relationship between any two concepts e.g. Stress Response and Gonadotropin Secretion.

The following example illustrates how the fuzzy system works to modulate the ontology relation *increases* between two concepts of Stress Response and Gonadotropin Secretion based on receiving evidence from literature results.

The agent initially identifies each type of research results (TRR) which are reported in the selected article conclusions or abstract sections and calculates their percentage (LOP) of appearing in a given set e.g. 100 articles. The result of such computation is used to fuzzify the antecedent inputs. Then, in the next stage, conditional on the obtained value of each input, the output value is determined according to the fuzzy rules. For example, if the system identifies that the percentage of the TRR which indicate a high positive conclusion (+*veH*) ranges between 70-100% (i.e. High LOP) of all the SRO theoretical statements, then the system output will take the value of *does*. In other words, according to Rule 1 of the Table 8.1, if the high positive conclusion (+*veH*) category of the TRR form 70-100% (High LOP) of all the SRO theoretical statements, then the previously *is highly likely to increase* relationship between the two concepts will be changed to *does increase*, i.e. “Stress Response *does increase* Gonadotropin Secretion”.

Since the corroborating, disproving, or neutral statements of the TRRs may appear in various linguistic forms, the system should employ logical operators of OR, AND (maximum, minimum) in order to collapse different statements of the same type into a predefined category of the TRR. For example, the *high positive conclusion* (+ve*H*) category of the TRR may be computed in the following way:

IF *“stress response* ***escalated*** *Gonadotropin secretion”* OR *“stress response* ***rises*** *Gonadotropin secretion”* OR *“stress response* ***has high positive association with*** *Gonadotropin secretion”* OR *“stress response* ***predicted*** *Gonadotropin secretion”* THEN *“Stress Response* ***does increase*** *Gonadotropin secretion”.*

In the abovementioned example, the high LOP is the Union (∪) of the LOP of the strong verifying statements which have used confirmative verbs of *escalated, rises*, *has high positive association with*, and *predicted*.

Notice that the statements after THEN are the ontology statements in the DO which are meant to be modified in proportion to the evidence obtained from the scientific literature.

8.4 Conclusion

In this chapter, we explained how the proposed EBEO methodology can be implemented to refine and modulate the relationships between two concepts in a scientific ontology such as the HSO in accordance with the scientific evidence. To perform this task, the EBEO employs an FIS which is embedded in an ASRA. The ASRA is an agent which uses the voting method of systematic review for the calculation of theory statements in scientific literature. ASRA deals with two separate ontologies: an SRO which is used for the annotation and extraction of relevant theory statements (i.e. evidence) in the literature; and the DO whose relationships will be modified in line with the obtained evidence.

Using this strategy, more accurate and evidential ontology relationships are predicted to be defined. This, in turn, may promise the establishment of evolving/evidence-based ontologies in scientific domains. In the next chapter, we present our evaluation results of the HSO and illustrate how the EBEO methodology can be implemented.

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Chapter 9 – Evaluation of the HSO and Illustration of the EBEO Methodology

9.1 Introduction

Ontology evaluation does not necessarily follow the conventional evaluation methods of empirical researches. In fact, ontology, regardless of the correspondence of its proposed conceptualization to reality, aims to create a shared framework for the purpose of common understanding and communication. Nevertheless, there are a number of evaluation methods that examine ontology with respect to criteria such as its conceptual coverage (Hartmann et al., 2005), reusability, consistency, clarity, coherence, minimal encoding bias, minimal ontological commitment, simplicity, and correctness (See Brank, Grobelnik, & Mladenic, 2005 for further details).

Different evaluation methods can be used for different purposes and applications (Brank et al., 2005). To evaluate the HSO, we have used two strategies:

1. *Implementation of the ontology*, and

2. *Concept coverage*

In this chapter, we also exemplify how the EBEO methodology can be implemented in practice, taking an example from the HSO.

9.2 Evaluation of the HSO

9.2.1 Implementation of the Ontology

Through the implementation, or execution, of the ontology we evaluate the *functional performance* of the ontology in practice. Here, functional performance refers to the utility of the ontology according to the following criteria:

1. Correct classification of a given concept in terms of its superclass-subclass relationships,
2. Offering a definition for that concept,
3. Illustrating its associations with other concepts, and
4. Restricting its context of application.

In the following example, using the ontology tool, we search the concept *Obsessive Compulsive Disorder* (OCD) to evaluate the functional performance of the HSO according to the abovementioned criteria.

As can be seen from Figure 9.1, entering the concept `ObsessiveCompulsiveDisorder` in the search section, the Protégé tool retrieves the related concept, illustrating its annotations, class descriptions, and its position in the hierarchy of the related superclass-subclasses.

- With respect to the first criterion, i.e. correct classification of the given concept, the HSO has correctly classified `ObsessiveCompulsiveDisorder`. This can be validated by referring to the well-established classification systems in the domain. For our example, we compared the classification of `ObsessiveCompulsiveDisorder` in the HSO to its classification in the MeSH. According to both classification systems, `ObsessiveCompulsiveDisorder` is a subclass of `AnxietyDisorders` (Figure 9.2). Respectively, consistent with MeSH classification system, `MentalDisorders` is the superclass of `AnxietyDisorders` in the HSO. However, in the HSO, `AnxietyDisorders` is also a subclass of `StressRelatedPsychiatricDisorder` (Figure 9.2).

- Regarding the second criterion, i.e. definition of the concept, the HSO has given a broadly-used definition of ObsessiveCompulsiveDisorder adopted from the MeSH concept descriptions (National-Library-of-Medicine, 2010) (Figure 9.3).

- The HSO also illustrates a number of relationships ObsessiveCompulsiveDisorder has with other concepts. These relationships are demonstrated in the description tab of the Protégé tool. As can be observed from Figure 9.4, ObsessiveCompulsiveDisorder is associated with the concepts CorpusCallosumAlteration, StressCause, StressMediator, HPAAxisHyperactivity, and Meditation in the following ways:

  - ObsessiveCompulsiveDisorder hasAssociationWith some CorpusCallosumAlteration
  - ObsessiveCompulsiveDisorder hasCause some StressCause
  - ObsessiveCompulsiveDisorder hasMediator some StressMediator
  - ObsessiveCompulsiveDisorder hasPositiveAssociationWith some HPAAxisHyperactivity
  - ObsessiveCompulsiveDisorder hasTreatment some Meditation

- Concerning the last criterion, i.e. restricting the application context of a given concept, the HSO has restricted the application or context of some of its theoretical statements (class descriptions). For example, the application of the statement "ObsessiveCompulsiveDisorder hasAssociationWith some CorpusCallosumAlteration" is restricted through the annotation of *context* (Figure 9.5). As the figure shows, the context annotation indicates that OCD *compulsive* rather than *obsessive* symptoms are associated with Corpus Callosum alteration (Friedlander & Desrocher, 2006; Rosenberg & Keshavan, 1998).

These examples in addition to the examples provided in Chapter 7 (formalization of the conceptualization) show that the implementation of the HSO is functional with respect to the abovementioned criteria. Nevertheless, a large number of concepts in the current version of the HSO still need refinement and enhancement to fulfil the evaluation criteria.

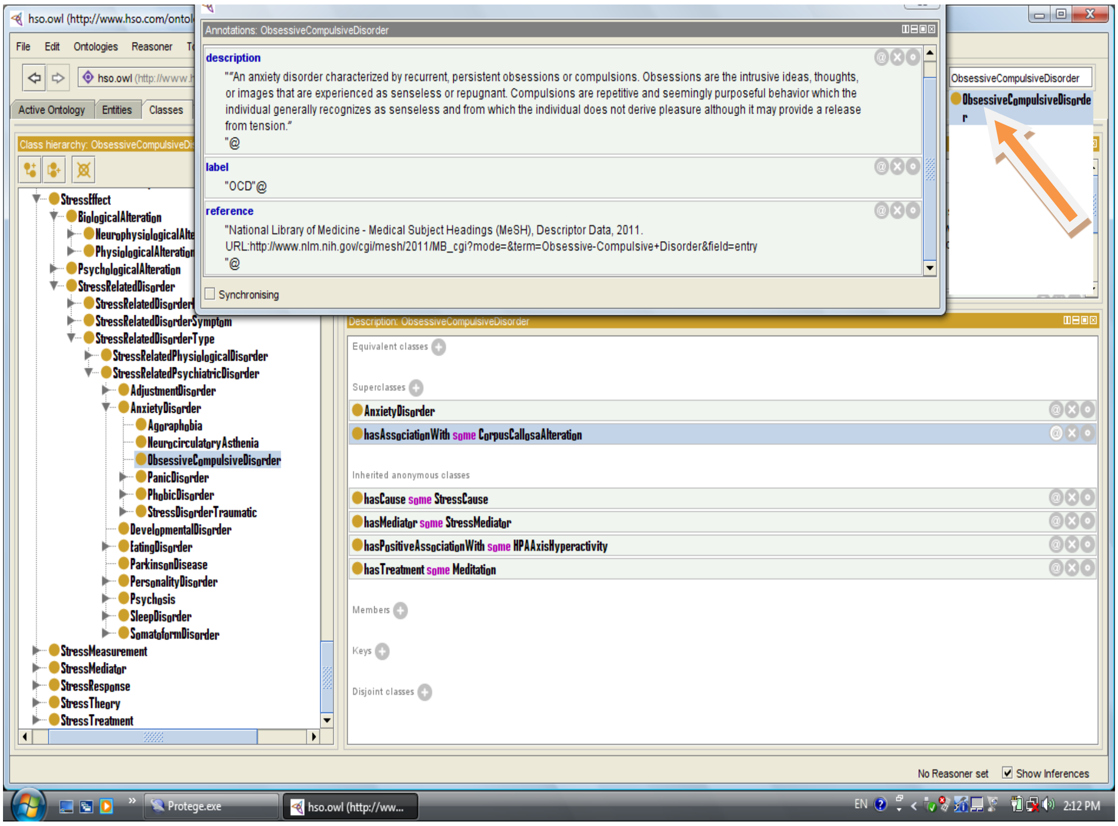

Figure 9.1. Retrieval of the class ObsessiveCompulsiveDisorder

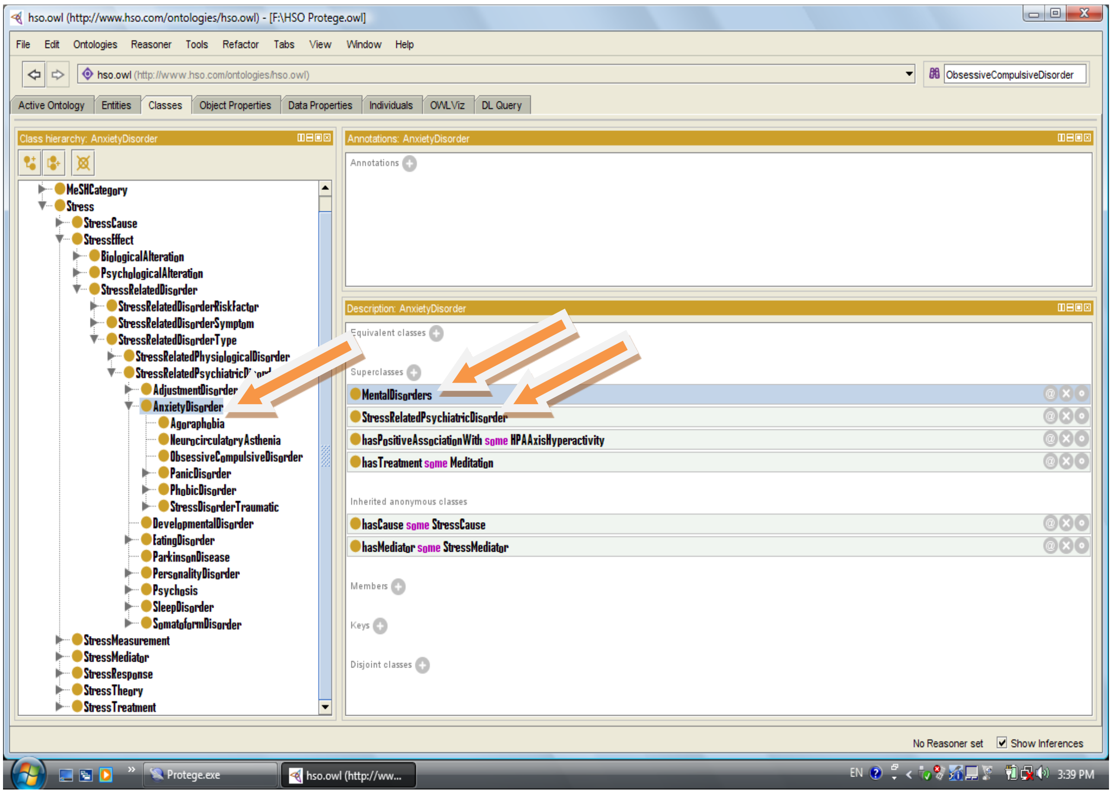

Figure 9.2. Superclasses of the class ObsessiveCompulsiveDisorder

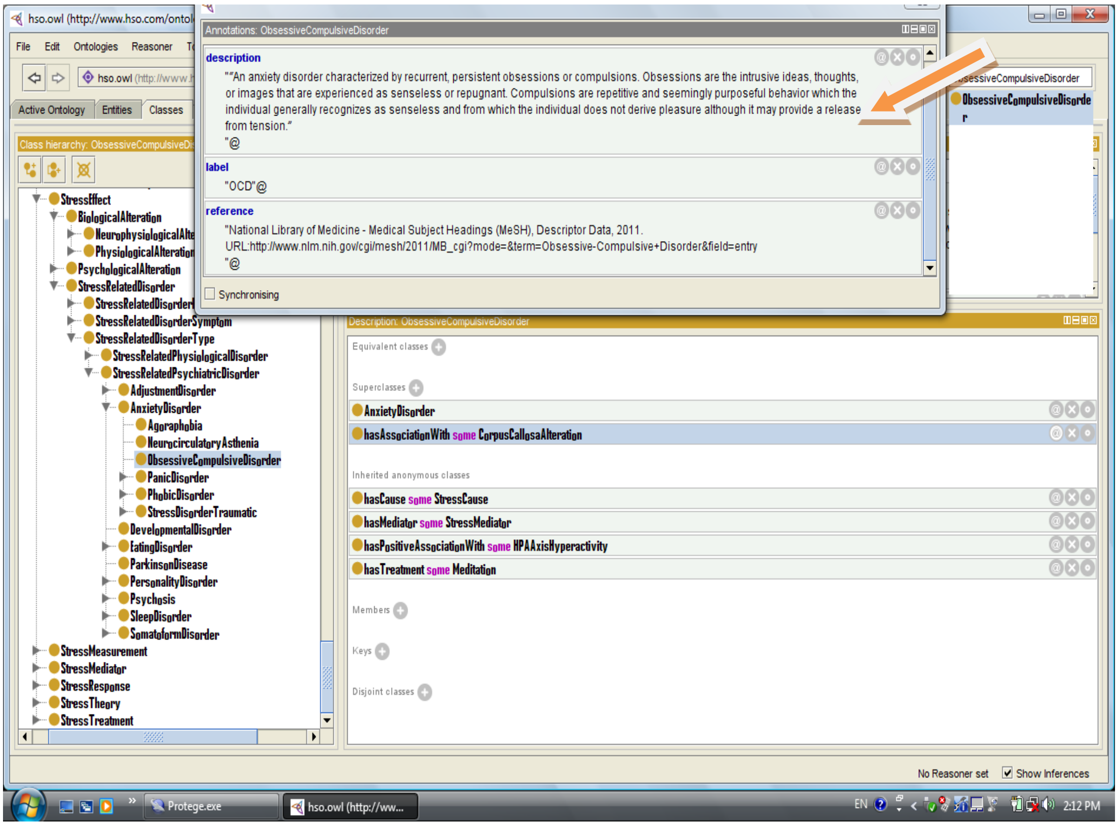

Figure 9.3. Definition of the class `ObsessiveCompulsiveDisorder` using annotations

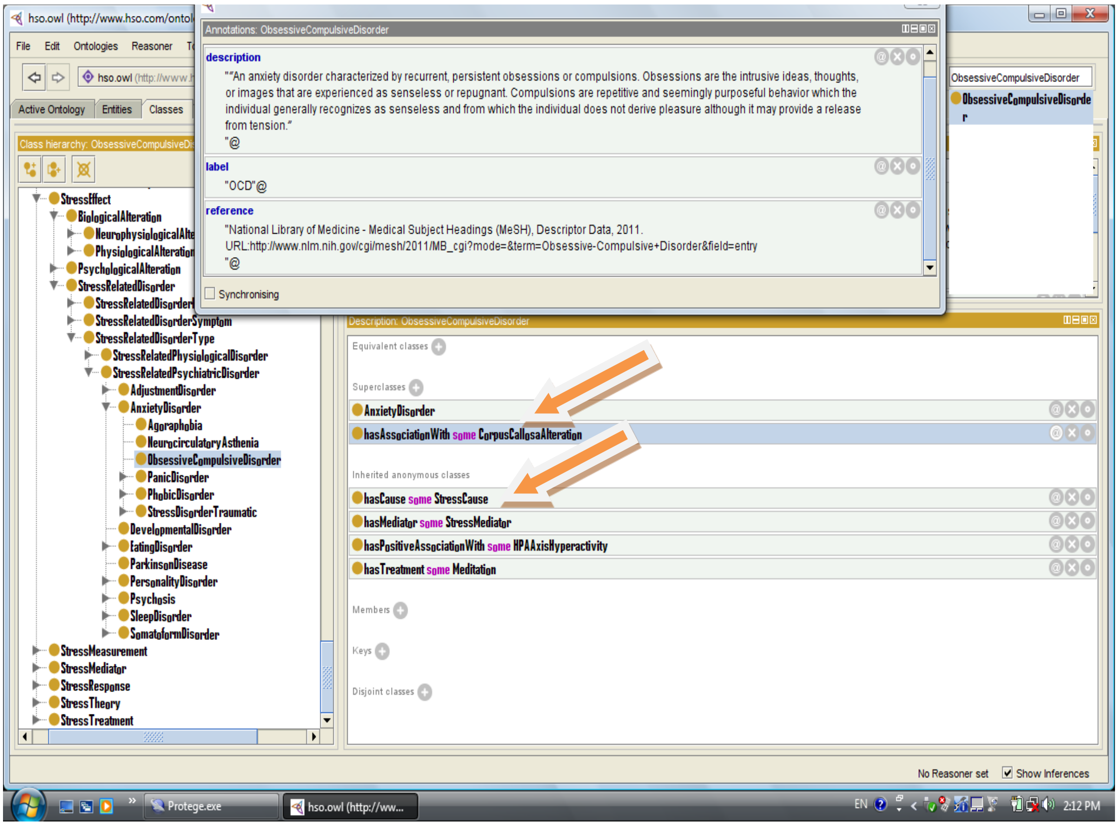

Figure 9.4. Description of the class `ObsessiveCompulsiveDisorder` via its links to other concepts

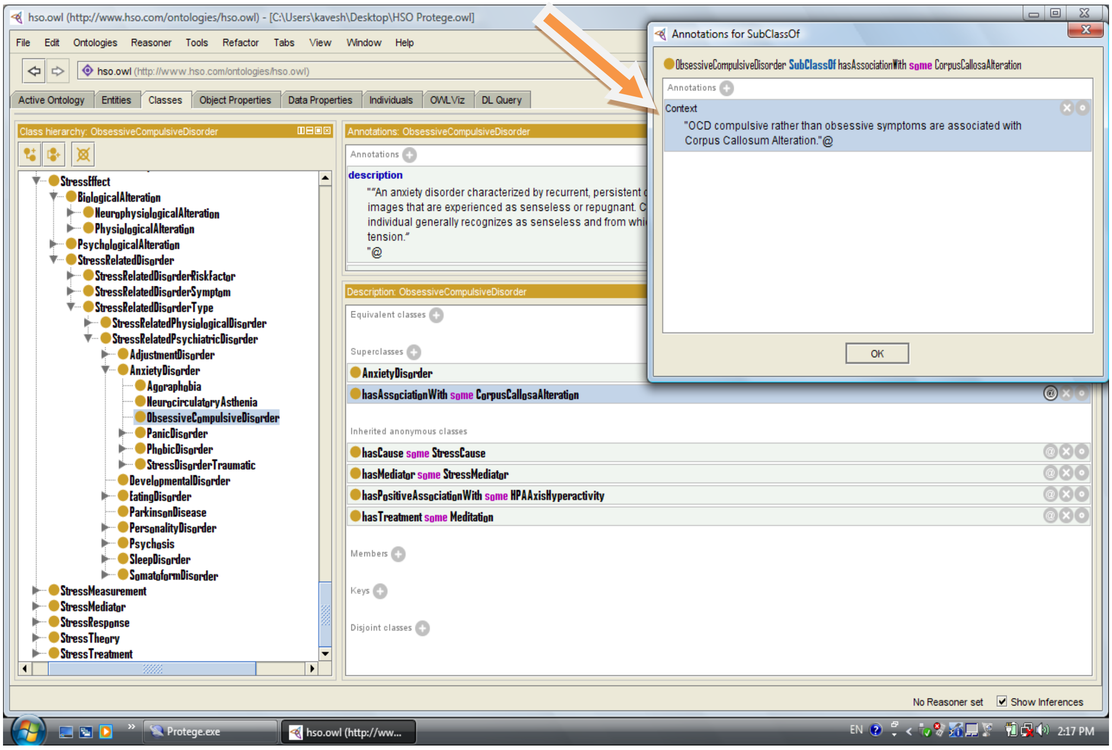

Figure 9.5. Restricting the application of the concept description via context annotation

9.2.2 Concept Coverage

The *concept coverage* method is a strategy by which we determine the percentage of the domain concepts which are covered (represented) by the ontology. This section elaborates on the process and results of our evaluation of the HSO.

Our evaluation method involves comparison of the concepts contained in the HSO with a selected source of data from the domain of stress. We chose two widely-used databases in the psychology and psychiatry domains, i.e. PsycARTICLES (ovid SP) and EMBASE (ovid) to extract and analyse a selected source of data for ontology evaluation. On 27/09/2010 we searched for the keyword *stress* in the PsycARTICLES database with an unlimited time range. The search engine offered a total of 5314 results from which 30 article abstracts were randomly selected using the systematic sampling method. The majority of the selected articles were related to various aspects of human stress. Likewise, on 29/09/2010 the EMBASE database was searched for the keyword *stress*. We limited the search results to article abstractions and selected the following subject headings:

Acute stress, Acute stress disorder, Chronic stress, Cognitive behavioural stress management, Early life stress, Emotional stress, Family stress, Life stress, Maternal stress, Mental stress, Physiological stress, Post traumatic stress disorder, Role stress, Social stress, Selye's stress theory, School stress, Parental stress, Perinatal stress, Stress strain relationship, Behavioural stress, Contact stress, Critical incident stress, Environmental stress, Interpersonal stress, Job stress, Lazarus theory of stress and coping, and Pharmacologic stress testing.

These subject headings were related to the HSO classes. The search engine found 114863 results. Similarly, 30 article abstracts were randomly selected from this data collection using the systematic sampling technique.

In the next stage, we examined these 60 article abstracts and extracted their stress-related concepts.

For example, the statement "*Thus, early postnatal handling appears to influence the development of the glucocorticoid receptor system in the hippocampus and frontal cortex*" (Meaney et al., 1985) from one of the abstracts was analysed in terms of its stress-related concepts. In this example, we identified the stress-related concepts of "*Early Postnatal Handling*", "*Glucocorticoid Receptor*", "*Hippocampus*", and "*Frontal Cortex*". Extracted concepts were placed under the seven sub-ontologies of the HSO according to their role and semantics. For example, in the above example, early postnatal handling, glucocorticoid receptor, hippocampus, and frontal cortex were placed under the category of Stress Mediator as all these concepts had to do with the mediation of stress response. Figure 9.6 illustrates the process of manual concept mapping for the above example.

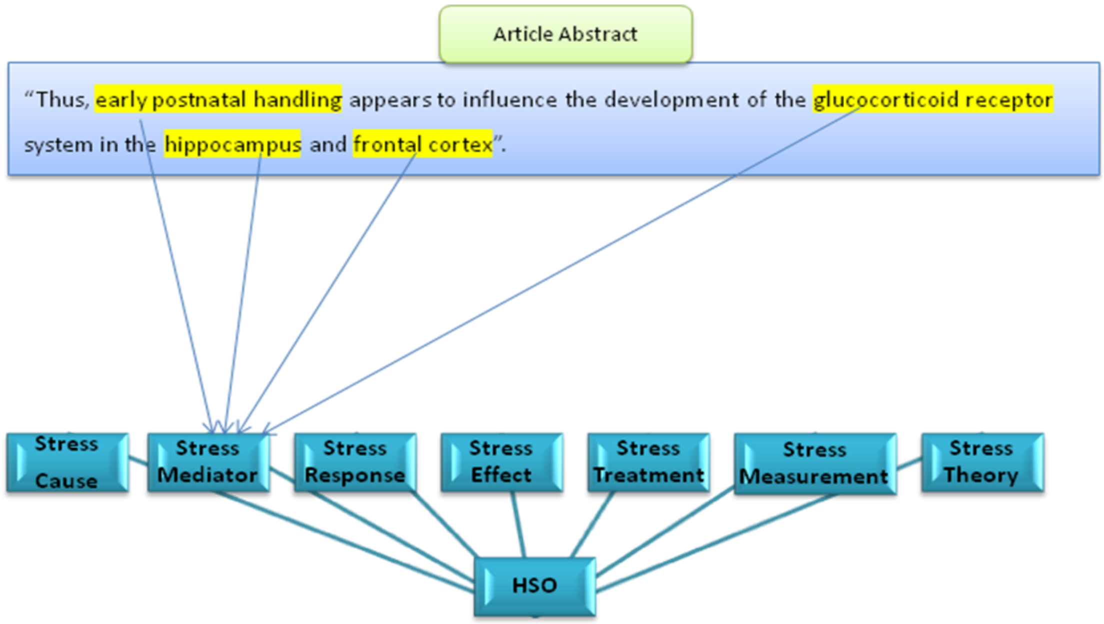

Figure 9.6. The mapping of the stress-related concepts in an article abstract into the HSO sub-ontologies

Table 9.1 represents the results of the concept mapping for the presented article abstract. As can be seen, there exist equal HSO classes for the concepts Glucocorticoid Receptor and Hippocampus. However, the concepts Early Postnatal Handling and Frontal Cortex have no equivalent or similar concept in the HSO. All mapping results are given in Appendix A of this thesis.

Table 9.1. Concept mapping of stress-related concepts in the presented article abstract

	Extracted Concept from the Article Abstract	**Its Equivalent or Similar HSO Concept**
1	Early Postnatal Handling	——
2	Glucocorticoid Receptor	Glucocorticoid Receptor
3	Hippocampus	Hippocampus
4	Frontal Cortex	——

The results of our concept analysis and mapping process are as follows:

1. We were able to fit almost all the extracted stress-related concepts under the predefined sub-ontologies of Stress Cause, Stress Mediator, Stress Response, Stress Effect, Stress Treatment, Stress Measurement, and Stress Theory. This shows that these general categories can form the upper-level hierarchy of many other taxonomical and ontological systems in the human stress domain.

2. After calculating the percentage of the extracted concepts that had an equal or similar HSO concept, the following results were obtained for each of the HSO sub-ontologies:

Table 9.2. Evaluation results. The percentages are approximate

HSO sub-ontology	The percentage of stress-related concepts in the databases which had equal or similar HSO concept
Stress Cause	61
Stress Mediator	68
Stress Response	100
Stress Effect	64
Stress Treatment	32
Stress Measurement	18
Stress Theory	100
Average	63

The calculated results (Table 9.2) show that for most of the extracted stress treatment concepts and stress measurement concepts, there is no equal or similar HSO concept. However, the HSO provides an average to full representation for other categories.

Overall, our evaluation results demonstrate that the current version of the HSO needs further refinement and evolution to incorporate more concepts and theories and be a more inclusive representation of the human stress domain.

9.3 Illustration of the EBEO Methodology

To exemplify the evaluation of the EBEO methodology, we explain how a given ontology relationship in the domain ontology evolves and changes in response to the evidence received from the Systematic Review Ontology (SRO).

For example, the relationship "*is likely to suppress*" in the ontology statement "*Cortisol is likely to suppress Immunity*" is refined in the Domain Ontology (DO) in the following way.

1. The above ontology statement is initially defined for the higher-level ontology, i.e. the SRO. The SRO also considers different synonyms and spellings of the words and concepts of the ontology statement as well as a set of similar statements which indicate different directions of high positive, positive, high negative, negative, or neutral as to the corroboration or refutation of the given theoretical statement. Table 9.3 gives a sample of the relevant statements that we may define for the above theoretical statement. These statements are only a limited sample of all the possible relevant statements in the scientific works.

Table 9.3. A Sample of Relevant Theoretical Statements in the SRO

Indication	Relevant Theoretical Statements stored in the SRO
High Positive	Cortisol suppresses Immune System
———	Cortisol causes Immune System Suppression
———	Glucocorticoids[1] suppress Immunity
———	Glucocorticoids cause Immune System Suppression
———	Cortisol has high positive association with Immune System Suppression
———	Immunity was suppressed by Cortisol
———	Cortisol hampers Immunity
Positive	Cortisol is likely to suppress Immune System
———	Immune System may be suppressed by Glucocorticoids
———	Immune System had moderated positive association with Cortisol Secretion
———	Immune Suppression was positively correlated with Glucocorticoid Secretion
———	Glucocorticoids are likely to hamper Immunity
———	Cortisol Secretion can probably hamper Immune System
———	Hypercortisolism had an Average correlation with Immune Suppression
———	Glucocorticoid Secretion is moderately correlated with Immune Suppression
Neutral	Cortisol had no significant effect on Immune System Suppression
———	Glucocorticoids had no considerable impact on Immune System Suppression
———	Glucocorticoids has no association with Suppressed Immunity
———	Cortisol has no correlation with Suppressed Immunity
———	Cortisol did not suppress Immunity
———	Immunity is not suppressed by Cortisol
———	Immune System was not hampered by Glucocorticoids
Negative	Cortisol is likely to increase Immune Activity
	Immune Activity is positively associated with Cortisol
	Cortisol Escalation was moderately correlated with Immune System Activity
	Immune System Activity may escalate in response to Glucocorticoid Secretion
	A Moderate positive correlation was found between Cortisol and Immune Activity
	Hypercortisolism was moderately correlated with the Increased Immune Activity
	Immune Activity may escalate in response to High Cortisol Levels
High Negative	Cortisol increased Immune System Activity

[1] Glucocorticoids in humans are called Cortisol.

———	Glucocorticoids stimulated Immunity
———	Immune System was stimulated by Cortisol
———	Cortisol had high negative association with Immune System Suppression
———	Glucocorticoids predicted Enhanced Immunity
———	Cortisol Secretion strongly predicted the Increased Immune Activity
———	Cortisol had high positive correlation with Immune Activity

In the next stage, these synonymous statements are used by the annotation tools, which are employed by the Automated Systematic Review Agent (ASRA), to indentify relevant texts in electronic databases, and annotate, retrieve, and store their accessible relevant theoretical statements in terms of their indication of the corroboration or negation of the DO ontological statement. The retrieved statements, then, are stored in a separate database on which the calculating tasks are performed.

For example, the ASRA annotation tools select and retrieve 10 relevant articles which contain empirical reports about the relation between cortisol and the immune system. Of the 10 selected articles, the following theoretical statements (presented in Table 9.4) are identified and retrieved:

Table 9.4. The retrieved theoretical statements from the selected articles

Article Number	**The Retrieved Theoretical Statements**	**Indication**
1	Cortisol suppresses Immune System	High Positive
2	Glucocorticoids has high positive association with Immune System Suppression	High Positive
3	Cortisol had no significant effect on Immune System Suppression	Neutral
4	Immunity was suppressed by Cortisol	High Positive
5	Cortisol causes Immune System Suppression	High Positive
6	Immune System was stimulated by Cortisol	Negative
7	Cortisol hampers Immunity	High

		Positive
8	Glucocorticoid Secretion is moderately correlated with Immune Suppression	Positive
9	Cortisol Secretion strongly predicts Immune System Suppression	High Positive
10	Glucocorticoids suppress Immunity	High Positive

In the next stage, these retrieved theoretical statements, which are stored in the ASRA repository, undergo a statistical analysis to compute the percentage of statements which indicate positive, neutral, or negative connections between the two concepts, i.e. cortisol and immunity.

The developed *Fuzzy Inference System* (FIS) (explained in Chapter 7) in the ASRA, then modifies the DO ontological relation of "*suppress*" in proportion to the result of this calculation.

For the above example, the ASRA calculates that 7 out of the 10 articles (70%) of the retrieved statements indicate a high positive conclusion (*+veH*) for the ontological statement "*Cortisol is likely to suppress Immunity*". This percentage corresponds to the High LOP (Level of Proof) component in the input. Figure 9.7 illustrates the related membership functions of this percentage.

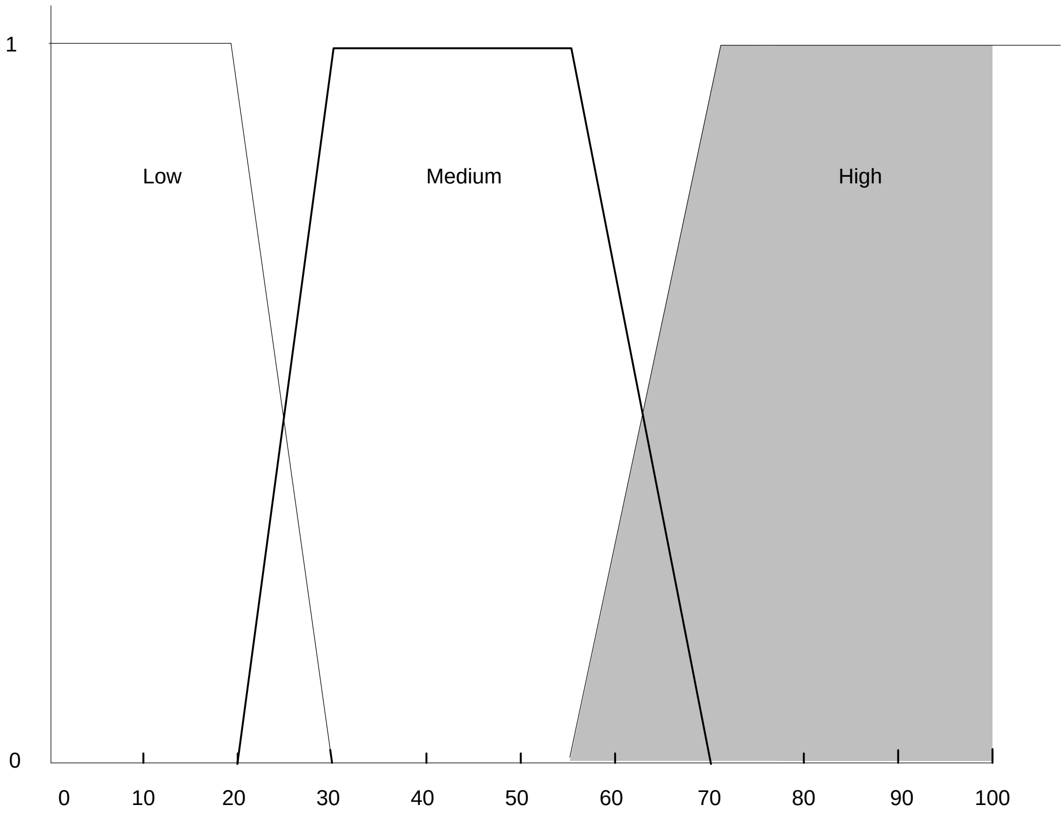

Figure 9.7. The numeric and linguistic Level of Proof (LOP) for the ontological statement "Cortisol is likely to suppress Immunity" in the simulation

Therefore, according to the fuzzy rule "IF *TRR*= *+veH* and *LOP*= *H* THEN Output = *does*", the ontology relation (fuzzy rule output) "*is likely to suppress*" in the DO becomes "*does suppress*" i.e. "*Cortisol does suppress Immunity*".

This means that there is sufficient evidence in the literature to indicate the existence of a strong positive association between Cortisol and Immunity along the relationship *Suppress*. The modified ontology relationships, thus, can inform the ontology users of the latest state and level of evidence for the abovementioned ontological statement, thereby assisting them with various decision making scenarios e.g. within clinical situations.

Therefore, when the level of evidence changes, i.e. new research reports are published in the literature, the FIZ reconsiders all the ontological relationships, adjusting them to the new level of proof.

9.4 Conclusion

The HSO was evaluated using an implementation method and a concept coverage strategy. Via the ontology implementation for the classification and description of a given concept, we illustrated that the HSO is a functional tool for the organization of stress knowledge. Moreover, our evaluation results showed that the HSO sub-ontologies provide a reasonable classification of the stress-related concepts in the literature since we were able to place almost every concept under one or more category of these sub-ontologies. Furthermore, the results showed that the HSO needs more refinement and evolution to incorporate more concepts embedded across databases. In this chapter, we also illustrated how the EBEO methodology is implemented in practice. In the next chapter, we recapitulate this thesis and touch on a number of limitations we have encountered so far. We will also outline the future directions.

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Chapter 10 – Recapitulation, Limitations and Future Work

10.1 Introduction

In this last chapter, we present a summary of the employed methodologies, the Human Stress Ontology (HSO) structure, and evaluation results together with the concluding points of our research work. We also consider some of the limitations we have faced in our research on the ontology of human stress as well as the foreseen limits of the proposed ontology evolution methodology. To conclude, we envisage the directions of the future work on the HSO and its potential applications, and offer some suggestions for further improvement and implementation of the Evidence Based Evolving Ontology (EBEO) methodology.

10.2 Recapitulation

This thesis described how we developed for the first time an ontology framework for the human stress domain. It also proposed a solution for the evolution and refinement of ontology relationships.

The HSO aims to provide a formal and interconnected framework for the existing concepts, their relationships, and theories within the domain of human stress so that the meaningful links and associations between dispersed concepts and theories can be viewed and apprehended effectively.

We also highlighted the rationale for grounding ontology relationships in evidence-based research results and enabling them to evolve in line with the emergence of new scientific discoveries and reports. In response to this need, the EBEO methodology was proposed as a potential solution for the refinement and evolution of ontology relationships in scientific ontologies. The following is a summary of the implemented methodologies, the HSO structure, and our evaluation results.

10.2.1 Recapitulation of the Implemented Methodologies

10.2.1.1 The Implemented Methodology for the Development of the HSO

We implemented the various stages of an ontology-building method which were adopted from DOGMA ontology engineering methodology (Spyns, Tang, & Meersman, 2008) and Knowledge Engineering Methodology (Noy & McGuinness, 2001; Uschold & Gruninger, 1996).

We started with the definition of our research vision statement which was a formal representation of knowledge about human stress in an ontological framework. Then, we identified our knowledge resources which included the Encyclopedia of Stress (Fink, 2007) as well as other texts and electronic journals in the fields of psychiatry and psychology.

After reviewing the literature relating to stress, we selected the relevant texts from which we could extract theoretical statements in the form of concepts and the relationships between them. We also used the MeSH categories and incorporated their stress-related concepts in the HSO.

Subsequently, we conceptualized and classified stress knowledge in the form of ontological statements which consist of concepts and relationships between them. We placed all concepts in one or more higher categories which fall under the predefined HSO sub-ontologies and/or MeSH categories.

Then, the conceptualized knowledge was formalized using the Protégé tool. Information about ontology concepts was added as class descriptions and/or metadata to the ontology tool. Protégé uses OWL language to define and describe concepts and their relationships. Finally, the designed ontology was evaluated using an ontology implementation method and a conceptual coverage technique.

10.2.1.2 The EBEO Methodology

The thesis also described our proposed solution for the refinement of ontology relationships based on the evidence obtained from the scientific literature. Our proposed methodology (EBEO) was as follows:

A Systematic Review Ontology (SRO) is implemented to identify relevant research results and extract theory statements from scientific articles. Then, the percentage of each type of theory statement in terms of its corroboration or disproof of a relationship between two specific concepts is calculated. The outcome of this calculation is the input for a Fuzzy Inference System (FIS) which is located in an Automated Systematic Review Agent (ASRA). Subsequently, the output is the refinement of ontology relationships in the domain ontology. In this way, we are able to define more evidence-based and evolving theoretical statements for scientific ontologies.

10.2.2 Recapitulation of the HSO Structure

The conceptualization and classification of the HSO were presented in a separate chapter where we explained the ontology structure and offered a review of stress knowledge. The structure of the HSO is made up of seven sub-ontologies, each with a number of related categories. The HSO sub-ontologies include: stress cause, stress mediator, stress response, stress effect, stress treatment, stress measurement, and stress theory. In order to enrich the HSO and utilize an already established medical ontology in our work, we included a specific category, dubbed MeSH category, where stress-related concepts from MeSH database were incorporated into the HSO.

Having reviewed a large number of research works on various aspects of human stress, we showed the complexity and multidimensionality of the stress phenomena. Stress can be caused by various physical, physiological, and psychological factors. However, the individual responses to the sources of stress, particularly psychological ones, vary depending on different physiological, psychological, and situational mediators. As a result, the occurrence of the same event may produce different health and functioning outcomes for different individuals.

The HSO also explained a number of stress-treatment strategies ranging from various psychotherapy techniques to pharmacologic agents and alternative therapies. We also discussed how different aspects of stressors, stress reactions, and their effects on the organism can be evaluated using a number of physiological techniques and psychological inventories. Stress theory was another major category of the HSO which incorporated a number of predominant theories in the domain of human stress.

10.2.3 Recapitulation of the Evaluation Results

We showed that the HSO can be implemented for different information retrieval and description purposes in the domain of human stress. Furthermore, almost all stress-related concepts in the randomly selected literature were able to be placed under one or more predefined sub-ontologies of stress cause, stress mediator, stress response, stress effect, stress treatment, stress measurement, and stress theory. Furthermore, a large percentage of stress-related concepts in the selected literature had equivalent or similar concepts in the HSO. We also showed how the EBEO methodology can be implemented.

10.3 Limitations

There are a number of limitations and restrictions in the development of the HSO and implementation of the EBEO methodology which need to be addressed in future works.

10.3.1 Limitations of the HSO

There were two main limitations in the development of the HSO:

1. Lack of consensual definition of some stress-related concepts, and

2. Lack of well-established relationships between stress-related concepts.

10.3.1.1 Lack of Consensual Definition of Some Stress-Related Concepts

The first limitation relates to the lack of expert agreement on the definition of some stress-related concepts. A far as the conceptualization of psychological concepts such as stress is concerned, experts from various disciplines have reported cases of contradiction, disunity, the existence of superfluous jargon (Driver-Linn, 2003; Yanchar, 2000), and lack of consensual definitions (Goldstein, 1995) for concepts and terms across numerous divisions of psychology.

In the stress domain, discrepancies regarding the identification and description of various aspects of stress have resulted in the emergence of different definitions for it. Although Selye held that stress is not an ambiguous concept, but a *real* and *concrete* phenomenon whose mechanisms can be identified clearly and objectively in medical and biological terms (Selye, 1985), the history of stress-related research seems to have refuted this. For example, recent studies have questioned the non-specific aspect of stress response (Pacák & Palkovits, 2001), despite Selye's emphasis of it.

Some reviewers have noticed that since the prominent work of Selye on physiological stress, the word 'stress' has emerged across a huge range of studies to imply different phenomena such as various deleterious environmental factors, the organisms' mental or physiological responses to such factors, or the consequent disorders as the result of dealing with those factors (Everly & Lating, 2002).

This lack of common and precise definitions in the stress domain has caused some researchers to consider different meanings for several identical concepts in diverse studies, or to adopt different terms to represent one concept across various research works. This, in turn, has impeded the integration of stress-related findings and results, leading some researchers to:

(1) equate stress with specific emotional states such as anxiety, fear, or anger in some studies (e.g. Leventhal & Tomarken, 1986) (Lobel & Dunkel-Schetter, 1990), and

(2) obtain unclear and inconsistent results when evaluating different aspects of stress causes or effects (Monroe, 2008) (Nasiri Khoozani & Hadzic, 2010).

Such limitations and controversies will be inevitably reflected in any ontology in the stress domain. Nevertheless, there can be still agreements between the small communities of experts in terms of the definition of the concepts they apply. The future work can consider methods to obtain more consensual definitions for abstract stress-related concepts.

10.3.1.2 Lack of Well-Established Relationships between Stress-Related Concepts

The more complicated a system is, the more difficult it is to explain its mechanisms. For example, it is easier to explain relationships between two physical entities than between two biological entities (Mitchell, 2003). Clearly, establishing a relationship between two psychological concepts such as stress and emotion seems to be even more complicated and controversial.

This issue is due to a number of reasons such as the ambiguity of concepts themselves (Hunt, 2005) and the context-dependency of the truthfulness of the relationship (Mitchell, 2003). This limitation applies to almost every ontology framework in domains such as psychology and the social sciences. The future work needs to consider the design of more advanced ontology languages and tools where all contextual aspects of concepts and their relationships can be represented.

10.3.2 Limitations of the EBEO Methodology

Regarding the proposed methodology for ontology evolution, there are some limitations regarding the accuracy and reliability of the voting method for the evaluation of research results.

The implementation of the voting system, although a simple task, is hardly a reliable strategy. This is mainly due to the fact that a thorough examination of diverse studies often uncovers different methodologies, contexts, age groups, or uncontrolled conditions which have influenced their produced results. Relying on a simple voting technique, therefore, is less likely to give a correct account of the final conclusions obtained from an amalgamation of research works (Stanley, 2001).

10.4 Future Work

In this section, we provide some suggestions and reports on how ontologies such as the HSO, ontology-based techniques, and several other knowledge engineering strategies can be helpful in human stress research and practice. We also present some suggestions on how our ontology evolution methodology can prospectively be implemented and refined. The future work of this project can consider the assessment, implementation, and realization of these proposals.

10.4.1 Potential Applications of the HSO

Overall, we suggest that the application of the HSO in stress domain is likely to help stress researchers by:

1. Facilitating conceptualization and theorization of stress-related phenomena;
2. Facilitating measurement of stress-related phenomena;

3. Assisting in therapeutic and treatment situations; and
4. Facilitating information retrieval of stress knowledge.

10.4.1.1 Potential Application of the HSO in Conceptualization and Theorization of Stress-related Phenomena

The HSO has the potential to help researchers undertake more evidence-based, inclusive, and reliable conceptualization and theorization of stress-related phenomena. This objective may be achieved in the following ways:

10.4.1.1.1 Facilitation of Evidence-based Conceptualization of Stress-related Phenomena

It has been emphasized by some researchers that scientific conceptualization and theorization must be based on scientific evidence (Sabb et al., 2008; Zajonc, 1984). Regarding the need for evidence-based conceptualization in some areas of stress research, we can apply ontology-based techniques to combine data and evidence about various aspects of a certain concept, strengthening our conceptualization by providing supporting evidences from other relevant genetic, psychometric, or neurophysiological studies. Such corroborating proofs can be discovered as common patterns by ontology-based data mining methods or be identified by other knowledge engineering techniques such as annotation knowledge bases[1].

For example, in a recent work, Sabb et al (2008) designed a collaborative annotation knowledge base as a reliable categorization system in order to catalogue empirical findings about cognitive *endophenotype* selection which can be applied in molecular psychiatry research. *Endophenotypes* are those cognitive constructs which supposedly play an intermediary role between syndromal aspects and genetic levels. They have been suggested to cover lack of specificity between current syndromal categories and treatment and genetic

[1] Annotation knowledge bases are used for generation of metadata on the top of which other applications can be employed for intelligent storage, categorization, retrieval, and presentation of the users' documents.

findings across psychopathology studies. However, only theoretical definitions exist for the real structure of such cognitive constructs. To obtain more evidence-based indicators for these theoretical constructs, we can consider existing information about their heritability, neurophysiological, and psychometric correlates. Results of empirical studies relevant to genetic and psychometric correlates of a few cognitive constructs were collected in a database to provide a collaborative knowledge-building foundation which is likely to facilitate codification of empirical evidence for phenotype selection (Sabb et al., 2008).

10.4.1.1.2 Provision of an Inclusive Overview of all Related Research Findings and Theories

With regard to theorization, ontology can lessen the problem of exclusive accumulation of data by distinct theories by gathering supporting or opposing data from works of disparate theories into one framework. It is also able to store competing theories in distinct contexts, giving explicit explanations about the conditions under which a given theory can work more effectively. Continuous refinement and evolution of an ontology with new data about emerging findings and theories will help supporters of one theory to remain aware of new discoveries in other relevant and even seemingly irrelevant (but insightful) theories (Nasiri Khoozani, Hussain, Dillon, & Hadzic, 2010).

Notwithstanding the existence of explicit discrepancies among various theories, it is still possible to establish dialogue and identify some shared elements among them (Hunt, 2005). Furthermore, it has been emphasized that participation in cumulative and collective science is the *modus operandi* of scientific practice in the 21st century (Reis, 2007).

In the domain of *interpersonal relationships*, for instance, there have been several proposals for cross-disciplinary theorization through which different directions of interpersonal analyses can be integrated (Berscheid, 1999).

In this regard, Reis (2007) in his distinguished scholarly article points to the lack of necessary infrastructure (e.g. specialized technology) for undertaking such efforts in *relationship* *science*. Accordingly, the difficulty of intertwining different theories and results into a cohesive account has resulted in some studies, initially designed to investigate the same phenomenon, being diversified in their scope. As a possible integrative solution to such disparities, the idea of search for *central organizing principles* has been suggested. Central organizing principles are those core ideas or similar concepts which frequently appear across various research areas. Such key concepts, when represented in a web of theories and findings, can assist researchers to identify commonalities and gaps across a variation of theory constructs, find relevant links, fit incrementally their research findings into other existing theoretical explanations, provide context for various applications, and, by supplying rich descriptive databases and taxonomies, develop more fact-based and valid theories (Reis, 2007). For example, the adoption of a collectivistic approach by relationship science can assist researchers to recognise various mediating and moderating variables (e.g. gender, age, ethnicity, belief system) which are likely to influence their subject of study in different contexts. It can also prompt the implementation of effective conceptual advances and budding technologies which are being developed by other fields of study such as biology. Furthermore, awareness of the recent advances occurring in related disciplines such as the biological sciences can help investigators find meaningful links between certain relationship phenomena and their underlying biological mechanisms (Reis, 2007).

Even though the importance of having integrated and cross-disciplinary theorization in psychology has been recognized, no framework or basic infrastructure (e.g. specialized technology) has yet been developed to support this vision (Reis, 2007).

We propose Reis's (2007) proposition on "*organizing research findings around the central organizing principles*" can implement ontology as a facilitating tool and technological substructure. Such central organizing factors can be identified by data-mining and annotation tools should the results of research works and theory explanations be represented as ontology facts or statements.

By reducing theory elements into formal facts, we may be able to find common elements among different theories, facilitating the process of theory integration. Ontology in this sense can provide various theories with an insightful dialogue. Work on the implementation and application of ontology for the abovementioned initiatives can be an interesting and promising task.

10.4.1.2 Potential Application of the HSO in Measurement of Stress-related Phenomena

Another potential application of the HSO and similar ontologies, which deserves future work, is in the process of measurement of stress-related phenomena such as stress causes or effects.

Overall, a formal and consensual conceptualization, such as an ontology, for stress-related concepts can potentially help researchers design more consistent measurement tools in terms of "what attribute a certain test does really measure". For example, the criteria for the inclusion of each test item can be obtained from the ontological definition of that item in the related ontology. In fact, the notion of ontology requires researchers to make their measurement tools for evaluation of a certain attribute congruent with the definition and conceptualization of that attribute, irrespective to whether they offer an accurate account of the real nature of those characteristics.

For example, some researchers aiming to measure the quantity or quality of stress in individuals may end up evaluating *stressors* instead of *stress response*. In such situations, mapping of the test items to their predefined definition in the HSO can potentially resolve those controversial inconsistencies. Here, even though a predefined definition or conceptualization does not actually correspond to the reality of the evaluated entity, the linkage of the test items with a clear and agreed conceptualization framework can prevent the employment of contradictory or unsuitable test items, and discover overlaps between them. Therefore, the context-based formal facts in an ontology such as the HSO can be used as a basis for the development of more valid psychometric tests and inventories. In this way, ambiguous, interfering, or irrelevant items (e.g. stressor measuring items included amongst items measuring stress-response) can be recognized and separated out by juxtaposing them with items applicable in relevant contexts.

The implementation of ontology for this purpose is likely to facilitate the process of test invention and validation in psychology and psychiatry. On these grounds, we might also be able to automate the process of test invention and validation through the design and employment of intelligent agents in this field. For instance, an automated agent as such may have the potential to assist researchers or clinicians determine the percentage to which a certain test is associated with a specified concept (Nasiri Khoozani & Hadzic, 2010).

Furthermore, ontology-based knowledge systems can supply researchers and clinicians with efficient and sufficient information about the selection of the most suitable test for a given situation. For example, an intelligent interface agent[2], in the form of a decision support system, can be designed to receive users' requests (e.g. What is the most appropriate test for situation *X*?*)* and present them with the most suitable test available in addition to all other necessary information pertaining to its method of application, validity and reliability scores, and its predefined subjects.

10.4.1.3 Potential Application of the HSO in Therapeutic and Prevention Situations

The HSO may also have potential applications in diagnostic and therapeutic situations. There have been proposals for the implementation of ontology-based tree mining algorithms in psychiatric situations where efficient and multi-dimensional analysis of patients' semi-structured data is required. Reportedly, such algorithms can mine both genetic and environmental factors which are likely to contribute to the development of mental illnesses (Hadzic, Hadzic, & Dillon, 2008).

Ontology-driven knowledge can also facilitate the development of preventative and intervention strategies in the mental health domain. Hence, comprehensive, cohesive, and easy-to-retrieve representation of mental health knowledge in the form of an ontology can assist researchers and clinicians to identify various causes and mediators of psychiatric disorders, thereby creating more evidence-based and effective intervention strategies. Furthermore, ontology can help clinicians to store and systematize knowledge and scientific explanations pertinent to causal, precipitating factors and potential treatment strategies of target disorders in distinctive sections in accordance with the context in which they operate. Given that there exist different effective intervention strategies for different situations and different individuals, an ontology-based multi-agent system[3], in the form of a decision

[2] Interface agents assist the user to formulate queries and in return can forward the retrieved and assembled information to the user.

[3] A multi-agent system incorporates a number of operating agents with mutual interactions. Multi-agent systems resolve a given problem by decomposing it into smaller sub-problems so that the task can be shared

support system, is likely to facilitate the selection of the best treatment technique for a particular situation or individual. This can be achieved by considering different situations or personality attributes as distinctive contexts for which specific prescriptions are more likely to be successful.

In some previous attempts, it has been suggested that knowledge-based systems can be applied in urgent therapeutic situations where the user has to find immediate therapeutic solutions without the presence of a therapist (Binik, Servanschreiber, Freiwald, & Hall, 1988; Velicer et al., 1993).

10.4.1.4 Potential Application of the HSO in Information Retrieval of Stress Knowledge

There have been previous proposals for the application of universally accessible databases in the management and retrieval of knowledge obtained from psychology research (e.g. Johnson & Sabourin, 2001). Reportedly, such data-sharing archives can store all data sets and provide researchers and scholars with free access and utilization.

The HSO can potentially facilitate the integration of heterogonous information resources within the stress domain and help experts manage the contents of different databases in relation to one another. The HSO and its related ontologies can potentially enable different information systems to interoperate with each other. It can also be a basis for the development of ontology-driven software tools for different information retrieval, analysis, and pattern-discovery purposes.

Another importance of the HSO, in this regard, is its applicability in the design of Semantic Web engines through which desired information can be retrieved, accessed, managed, and analyzed in an intelligent and meaningful way.

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among different agents such as interface agent, manager agent, information agent, and smart agent (Hadzic & Chang, 2008).

There is a need to develop specific information resources which are equipped with search engines having the capacity to look for the meaning of information, and not merely being limited to the appearance of a specific word in the text. To overcome such obstructions, search engines must be able to search for the meaning of information rather than be confined to performing keyword-based or string searches (as is the case with current search engines such as Google). A meaning-oriented or semantic search engine will go beyond the appearance of a specific word in the text, looking for clues to link it to other relevant concepts or entities.

Ontology has the potential to introduce meaning and context into our search so that the search engine can retrieve intended semantic, contextual, and relevant information for the researchers. Therefore, one of the future works of the HSO project can be the design of metadata and semantic search engines in order to streamline the retrieval of stress-related information.

10.4.2 Future Work on the EBEO Methodology

Methods of systematic review have advanced over the years to account for more reliable statistical analysis of the data. *Meta-analysis* is one of the most advanced methods of systematic review.

Being a quantitative method for research analysis purposes, meta-analysis implements a variety of statistical methods in order to bring together the empirical results of different studies which have used a multitude of data sets and methods. In this way, it purports to give more insight into the individual studies as well as explain, evaluate, and elucidate conflicting and controversial results of various research works (Stanley, 2001).

By considering individual research works as constituting parts of a bigger study which form one single and final result, meta-analysis aims to summarize the evidence as a whole in order to infer valid conclusions and generalizations (De Almeida Biolchini, Mian, Natali, Conte, & Travassos, 2007).

It would have been a promising project if we had been able to incorporate a meta-analysis automated agent into the ontology evolution methodology. However, this does not seem plausible mainly because a typical meta-analysis process requires researchers to have access to all data from every selected study, all the respective research methods employed, and information about various features of the contexts in which the studies were conducted.

A lot of time and manual labour is needed to access and retrieve information of interest from this conglomeration of data since current information resources and retrieval techniques are not able to extract them automatically.

Nevertheless, we suggest that future work can consider the establishment of specific databases where researchers can store, organize, and encode their data and information about various features of their study (e.g. context, study subjects, etc) in a shared framework. This framework can serve as a special data repository for the exploration of which different automated knowledge engineering techniques can be implemented. In this fashion, a hypothetical *meta-analysis agent* will be able to access, encode, categorize, and analyse information about the results of different studies and, in so doing, generate statistically reliable conclusions concerning the evidentiality of ontology relations between concepts. Subsequently, the corresponding ontology relationships in domain ontologies can be refined and evolved in line with the evidence obtained from the meta-analysis agent.

Moreover, results of different studies on the existence or lack of significance of a relationship between two concepts can be stored and categorized consistent with the predefined definitions and context of those concepts. For example, the system can request researchers to consider the correspondence of the investigated concepts in their work with the predefined definition and description of those concepts in the domain ontology. It can also offer researchers the opportunity to enrich their domain ontologies with newly investigated or created concepts when these are missing. In this way, other investigators will have the chance to learn about newly-arrived concepts and novel phenomena in their domain of interest, initiate their own investigation of those concepts, and add the results of their studies to the system.

10.5 Conclusion

The thesis was recapitulated and summarized in this last chapter. Furthermore, we explained how the lack of consensus regarding the definitions of some stress-related concepts, and the difficulty of establishing relationships between psychological phenomena, can impose limits on the HSO. Moreover, the limitations of a voting approach in the implementation of the EBEO were discussed.

We also emphasized the contribution that our research work has made in establishing the first ontology for the stress domain and proposed a feasible solution for the refinement and evolution of ontology relationships in scientific ontologies.

Our proposed future work is to develop effective strategies and techniques to address limitations effectively and practically. It will also consider the role of the HSO as a facilitating tool for the creation of more evidence-based, inclusive, and reliable conceptualization, measurement, and therapeutic systems for stress phenomena. We explained how the employment of ontologies such as the HSO and ontology-based techniques can provide researchers and clinicians with effective technology to access, analyze, and integrate the accumulating knowledge of humans stress. These suggestions, though intangible in part, can inspire researchers to consider further use of knowledge-engineering techniques in the psychology and psychiatry domains. Subsequently, the possibility of the incorporation of a meta-analysis agent in EBEO is proposed.

We hope the HSO will motivate researchers in the fields of psychology and psychiatry to consider the development of ontologies for various topics and applications.

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Appendix A – Tables of Evaluation Results

Table 1. Concept Matching of Stress Cause Sub-ontology

	Extracted Concept from the Databases	Its Equivalent or Similar HSO Concept
1	Caregiver Stress	Caregiving
2	Economic Crisis	Economic Depression
3	Loss of Economic Resources	—
4	Intimate Partner Abuse	—
5	Chronic Restraint	—
6	Job Strain	Job Stress
7	Daily Stresses	—
8	Daily Strains	—
9	Daily Hassles	Hassle
10	Demand	Demand
11	Job Stress	Job Stress
12	Crisis	Crisis
13	Natural Disaster	Natural Disaster Stressor
14	Trauma	Acute Trauma
15	Prolonged Mental Stress	Prolonged Stress Response
16	Sexual Assault	Sexual Assault
17	Job Demand	Work Concern
18	Sexual Abuse	Sexual Victimization
19	Childhood Sexual Abuse	Child Sexual Abuse
20	Domestic Abuse	Domestic Violence
21	Work Stress	Work-Related Stressor
22	Family Stress	Family Stressor
23	Job-Family Interference	—
24	Lack of Task Sharing	—
25	Maternal Deprivation	Maternal Deprivation

26	Stressful Life Events	Stressful Life Event
27	Uncontrollable Aversive Outcomes	—
28	Manifest Rejection	—
29	Maternal Stress	—
30	Task-Induced Stress	—
31	Immobilization Stress	Immobilization
32	Repeated Exposure to Stress	Exposure to Repeated Stimulus
33	Vulvodynia	—
34	Social Expectations	Social Expectations
35	Organizational Constraints	Organizational Stress
36	Terrorist Attack	Terrorist Crime
37	Deactivation Uncertainty	Deactivation Uncertainty
38	Workload	Job Stress
39	Psychosocial Stresses	Social Stressor
40	Panicogenic Inhalation	—
41	Fear of Predation	—
42	Seasonal Stressors	—
43	Multifetal Pregnancy Reduction	—
44	Fasting	—
45	Human Immunodeficiency Virus (HIV)	HIV
46	Acquired Immunodeficiency Syndrome (AIDS)	—
47	Loss	Loss

Table 2. Concept Matching of Stress Mediator Sub-ontology

	Extracted Concept from the Databases	**Its Equivalent or Similar HSO Concept**
1	Well-being	Well-being
2	Physiological Reactivity	Physiological Stress Reaction

3	Social Support	Social Support
4	Personal Control	Perceived Control
5	Emotional Expression	Emotional Expression
6	Emotional Suppression	—
7	Emotion Regulation	Emotion Regulation
8	Personal Resources	Personal Resource
9	Autonomy	Autonomy
10	Emotional Culture	—
11	Cultural Orientations (Individualistic vs. Collectivist)	—
12	Socioethnic Affiliation	—
13	Control	Perceived Control
14	Expressive Writing (EW)	—
15	Psychological Adjustment	—
16	Behavioral Adjustment	—
17	Seeing Self as Victim	—
18	Repetition Compulsion	—
19	Proactive Personality	—
20	Self-Efficacy	Self-Efficacy
21	Perceived Mastery	Mastery
22	Avoidant Encoding Style	—
23	Impaired Memory for Trauma Cues	—
24	Suicidal Behavior	Suicide
25	Coping Response	Coping Mediator
26	Coping Skills	Coping Strategy
27	Supportive Relationships	Supportive Social Connection
28	Cerebral Asymmetry	—
29	Corticosterone	Corticosterone
30	Problem-Solving Skills	Problem-Solving Skill
31	Glucocorticoid Receptor	Glucocorticoid Receptor
32	Early Postnatal Handling	—

33	Personality	Personality Mediator
34	Social Resources	—
35	Stress Resistance	Stress Resistance
36	Perceived Social Support	Social Support
37	Personality Hardiness	Hardiness
38	Perceived Family Support	—
39	Over Protection	—
40	Adrenal Medulla	Medulla
41	Dopamine	Dopamine
42	Sex Differences	Gender Related Mediator
43	Amygdala	Amygdala
44	Infra-limbic Cortex	—
45	Cerebral Lateralization	—
46	Cortical Asymmetry	—
47	Stress Adaptation	Adaptation Biological
48	5-HT Deficiency	—
49	Sympathetic Nervous System (SNS) Activity	Sympathetic Nervous System
50	Glutamatergic System	—
51	Hippocampus	Hippocampus
52	Dentate Gyrus	Dentate Gyrus
53	Hippocampal Neurogenesis	Neurogenesis Alteration
54	Endocrine System	Endocrine System
55	Parenting Skills	Parenting Skill
56	Maternal Care	Maternal Care
57	Gonadal Steroids	Gonadal Steroid
58	Adrenal Seroids	Adrenal Hormone
59	Sex Steroid Hormones	Gonadal Hormone
60	Cortisol Concentration	Cortisol Level
61	Coping Strategy	Coping Strategy
62	Denial	Denial
63	Avoidant Coping Style	Avoidant Coping Strategy
64	Neurotransmitters	Neurotransmitter

65	Serotonin	Serotonergic Neurotransmitter
66	Dopaminergic System	Dopaminergic System
67	GABAergic Cells	—
68	Personal History of Psychiatric Distress	History of Psychological Problem
69	Familial Psychiatric History	Family History of Psychopathology
70	Friend Support	Supportive Friend
71	Sense of Mastery	Mastery
72	Homeostasis	Homeostasis
73	Frontal Cortex	—
74	Glutamate Receptor Ligands	—

Table 3. Concept Matching of Stress Response Sub-ontology

	Extracted Concept from the Databases	**Its Equivalent or Similar HSO Concept**
1	Chronic Stress	Chronic Stress
2	Distress (Emotional Distress)	Distress
3	Perceived Stress	Stress Feeling
4	Pituitary-Adrenal Stress Response	HPA Stress Response
5	Fight or Flight Response	Fight Flight Response
6	Acute Stress	Acute Stress Response
7	Prolonged (Repeated) Stress	Prolonged Stress Response
8	Stress Response	Stress Response
9	Endocrine Stress Response	Endocrine Stress Response

Table 4. Concept Matching of Stress Effect Sub-ontology

	Extracted Concept from the Databases	**Its Equivalent or Similar HSO Concept**
1	Posttraumatic Stress Disorder (PTSD)	Posttraumatic Stress Disorder
2	Anger	Anger
3	Spatial Memory	—
4	Motivation for Reward	Motivation
5	Motivation to Explore	Motivation
6	Motor Ability	—
7	Functional Alteration	—
8	Neuromorphological Alteration	—
9	Physiological Alteration	Physiological Alteration
10	Emotional Exhaustion	—
11	Carotid Artery Atherosclerosis	Atherosclerosis
12	Cardiovascular Disease	Cardiovascular Disease
13	Mood Disturbance	Mood Disorder
14	Depression	Depression
15	Cardiac Output (CO)	—
16	Sleep Disorder	Sleep Disorder
17	Suicidality	Suicidal Thought or Intension
18	Learning	Learning
19	Suicide Attempts	Suicide
20	Self Esteem	Self Esteem
21	Cardiac Activity	Cardiovascular Function
22	Alexithymia	—
23	Illness Onset	—
24	Illness	—
25	Health	Health Alteration
26	Learned Helplessness	Learned Helplessness

27	Task Error	—
28	Transcriptional Changes	—
29	Gene Expression	Gene Expression
30	Cell Signalling	—
31	Dopamine Release	—
32	Neuroendocrine Activation	Neuroendocrine Stress Response
33	Stress-Related Disorders	Stress-Related Disorder
34	Mitochondrial Disorder	—
35	Ocular Myasthenia	—
36	Dementia	Dementia
37	Impaired Memory	Disrupted Memory
38	Impaired Learning	Learning Deficit
39	Panic Disorder	Panic Disorder
40	Negative Emotional States	Negative Emotion Reaction
41	Fear	Fear
42	Sexual Arousal	—
43	Hyperthermia	—
44	Anxiety Disorder	Anxiety Disorder
45	Stress-Related Behaviors	—
46	Higher Postpartum Cortisol Levels	High Cortisol Level
47	Higher Prepartum Pregnanediol-3-Glucoronide Levels	—
48	Immune Function	Immune Function
49	Infection	Infection
50	Reproduction	Reproduction Alteration
51	Neurocognitive Deficits	Cognitive Deficit
52	Schizophrenia	Schizophrenia
53	Executive Function Deficit	—
54	Schizophrenia Relapse	Schizophrenia Relapse Episode
55	Psychotic State	Psychosis

56	Neurotoxicity	Neurotoxicity
57	Neuronal Degeneration	Neuronal Death
58	Hypotension	Hypoactive Stress Response
59	Digestive Enzyme	—
60	Enzymes Activity Change	—
61	Motor Activity	—
62	Hostility	Hostility
63	Vascular Entrapment	Vascular Disease
64	Migraine	Migraine Disorder

Table 5. Concept Matching of Stress Treatment Sub-ontology

	Extracted Concept from the Databases	**Its Equivalent or Similar HSO Concept**
1	Cognitive-Behavioral Interventions (CBIs)	Cognitive Behavioural Therapy
2	Stress Management Skills	Stress Management
3	Psychodynamic Peer Support Group Meetings	—
4	Didactic Experiential Group Instruction Program	Didactic Teaching Technique
5	Directed Forgetting of Trauma Cues	—
6	Resource Mobilization	—
7	Circuit Weight Training Programs	—
8	Emotion-Focused Therapy	—
9	Dexamethasone	—
10	Cholinergic Medication	—
11	Psychosocial Counselling	—
12	Anxiolytics	Benzodiazepine
13	Psychotropic	Antipsychotic
14	Chlordiazepoxide	Chlordiazepoxide
15	Alprazolam	Alprazolam
16	Buspirone	Buspirone

17	Glutamatergic Agents	—
18	Pharmacological Treatments	Pharmacologic Medication
19	Antidepressants	Antidepressant
20	N-methylaspartate (NMDA)	—
21	Moclobemide (MOC)	—
22	Serotoninergic Antagonists	—
23	Atypical Antipsychotics	Atypical Antipsychotic
24	Glutamatergic Agonists	—
25	Imipramine	Imipramine
26	Doxepine	—
27	Haloperidol	—
28	Amphetamine	Amphetamine
29	Methylglucamine Orotate	—
30	Beta-Casomorphin Derivative (BCH 325)	—
31	mGlu1 Receptor Antagonist LY456236	—
32	mGlu2 Receptor Potentiator LY566332	—
33	mGlu8 Receptor Agonist (S)-3,4-Dicarboxyphenylglycine	—
34	Competitive NMDA Receptor Antagonist LY235959	—
35	AMPA Receptor Antagonist GYKI-52466	—
36	Glycine Transporter-1 (GlyT-1) Inhibitor ALX-5407	—
37	AMPA Receptor Potentiator LY451646	—
38	iGlu5 Kainate Receptor Antagonist LY382884	—
39	$Glycine_B$ Receptor Partial Agonist d-Cycloserine	—
40	GlyT-1 inhibitor ORG-24461	—

Table 6. Concept Matching of Stress Measurement Sub-ontology

	Extracted Concept from the Databases	**Its Equivalent or Similar HSO Concept**
1	Hamilton Depression Rating Scale	—
2	Suicide Subscale	—
3	Schedule of Recent Events	Schedule of Recent Experiences
4	Lactate Stress Test	—
5	Electrodermal Response	Electrodermal Technique
6	Frontalis EMG	—
7	Self-Report	—
8	Brief Symptom Inventory (BSI)	—
9	Immunohistochemistry	—
10	Delayed-Type-Hypersensitivity (DTH)	—
11	Radiotelemetric Transmitter	—

Table 7. Concept Matching of Stress Theory Sub-ontology

	Extracted Concept from the Databases	**Its Equivalent or Similar HSO Concept**
1	Conservation of Resources (COR)	Conservation of Resources Theory
2	Karasek's Demands-Control Model of Stress	Demand Control Support Model
3	Diathesis-Stress-Hopelessness Model of Suicidal Behavior	Diathesis Stress Model of Depression

Appendix B – Titles of the Sample Articles

Table 1. The Sample Article Titles from PsycARTICLES Database

	Article Number	Article Titles
1	177	The longitudinal ramifications of stroke caregiving: A systematic review
2	354	Psychological impact of an economic crisis: A Conservation of Resources approach
3	532	Intimate partner abuse and PTSD symptomatology: Examining mediators and moderators of the abuse-trauma link
4	709	Meta-analysis of cognitive-behavioral interventions on HIV-positive persons' mental health and immune functioning
5	886	A rural perspective on health care for the whole person
6	1063	Chronic stress impairs spatial memory and motivation for reward without disrupting motor ability and motivation to explore
7	1240	Must "Service With a Smile" Be Stressful? The Moderating Role of Personal Control for American and French Employees
8	1417	Cultural Orientation, Ethnic Affiliation, and Negative Daily Occurrences: A Multidimensional Cross-Cultural Analysis
9	1594	Experiences of Demand and Control in Daily Life as Correlates of Subclinical Carotid Atherosclerosis in a Healthy Older Sample
10	1771	A pilot study of the effects of expressive writing on psychological and behavioral adjustment in patients enrolled in a Phase II trial of vaccine therapy for metastatic renal cell carcinoma
11	1948	Countertransference issues in crisis work with natural disaster victims
12	2126	Physiological activity during a prolonged mental stress task: Evidence for a shift in the control of pressor reactions
13	2303	Sleep disorder, depression and suicidality in female sexual assault survivors
14	2480	Minimizing strain and maximizing learning: The role of job demands, job control, and proactive personality
15	2657	Directed forgetting of trauma cues in adult survivors of childhood sexual abuse with and without posttraumatic stress disorder
16	2834	Culturally competent interventions for abused and suicidal African American women
17	3011	Dual-earner families: The importance of work stress and family stress for psychological well-being
18	3188	Asymmmetry of forehead temperature and cardiac activity
19	3365	Psychological and physical benefits of circuit weight training in law enforcement personnel
20	3543	PTSD and alexithymia: Importance of emotional clarification in treatment
21	3720	Health psychology: The science and the field
22	3720	Health psychology: The science and the field
23	3897	Plasma corticosterone fluctuations in an infant-learning paradigm
24	4074	Problem-solving skills in suicidal psychiatric patients

25	4251	Early postnatal handling alters glucocorticoid receptor concentrations in selected brain regions
26	4428	Personality and social resources in stress resistance
27	4605	Psychological intervention and reduced medical care utilization: A modest interpretation
28	4783	Learned helplessness: The result of uncontrollable reinforcements or uncontrollable aversive stimuli?
	4960	Shifts in child-rearing attitudes linked with parenthood and occupation
29	5137	Interactions between display gain and task-induced stress in manual tracking
30	5314	Review of A Study of Ethical Principles

Table 2. The Sample Article Titles from EMBASE Database

	Article Number	**Article Titles**
1	3829	Reproductive ecology and the endometrium: Physiology, variation, and new directions
2	7658	Analysis of signalling pathways triggering transcriptional changes in adrenal medulla with single and repeated stress
3	11486	Lateralized sex differences in stress-induced dopamine release in the rat
4	15315	Mitochondrial disorder mimicking Ocular myasthenia
5	19144	Effect of 5-HT and postsynaptic 5-HT1A on the mood and recogniztion of the repeated restraint stress in rats
6	22973	Review of the literature on the psychoemotional reality of women with vulvodynia: Difficulties met and strategies developed
7	26801	Back to basics: assessment, communication, caring, and follow-up: a lesson from a couple's journey with multiple myeloma
8	30630	The impact of deactivation uncertainty, workload, and organizational constraints on reservists' psychological well-being and turnover intentions
9	34459	Psychooncology: Concepts and tasks of a young discipline
10	38288	Sex differences in response to a panicogenic challenge procedure: An experimental evaluation of panic vulnerability in a non-clinical sample
11	42116	Psychophysiological sexual arousal in women with a history of child sexual abuse
12	45945	Pharmacological characterization of stress-induced hyperthermia in DBA/2 mice using metabotropic and ionotropic glutamate receptor ligands
13	49774	Use of the diagnostic criteria for psychosomatic research in oncology
14	53602	Moclobemide up-regulates proliferation of hippocampal progenitor cells in chronically stressed mice
15	57431	The role of the endocrine system in baboon maternal behavior
16	61260	Sex differences in photoperiodic and stress-induced enhancement of immune function in Siberian hamsters
17	65089	Patterns of neurocognitive deficits and unawareness of illness in

		schizophrenia
18	68918	Comments on the FRAMIG 2000 study
19	72746	Neurobiological perspective of schizophrenia
20	76575	The use of the Mainz Dortmund dose model (MDD) in a case-control study of lumbar spine disease
21	80404	Posttraumatic stress disorder in older adults: A conceptual review
22	84233	Prophylactic analgesia in functional endoscopic sinus surgery - Hemodynamics, surgical conditions, stress response
23	88061	Implications of hormesis for biomedical aging research
24	91890	The review and evaluation of viscoelastic models for collagen fiber during constant strain rate loading
25	95719	The current status of multifetal pregnancy reduction
26	99548	The activity of digestive enzymes in the digestive and non-digestive organs during stress exposures
27	103377	Finger joint force minimization in pianists using optimization techniques
28	107205	Effects of BCH 325 (Pro-D-Phe-Pro-Gly) on open field behavior after chronic stress procedure
29	111034	Infection with human immunodeficiency virus and vulnerability to psychiatric distress. A study of men with hemophilia
30	114863	Hypothesis: Stress induced vascular entrapment and migraine

Appendix C –List of Publications

1. Nasiri Khoozani, E., & Hadzic, M. (2010). Designing the human stress ontology: A formal framework to capture and represent knowledge about human stress. *Australian Psychologist, 45*(4), 258 - 273.

2. Nasiri Khoozani, E., Hussain, O., Dillon, T., & Hadzic, M. (2010). *Evidence/Discovery-Based Evolving Ontology (EDBEO)*. Paper presented at the 23rd IEEE International Symposium on Computer Based Medical Systems, Perth, Australia.

3. Nasiri Khoozani, E., & Hadzic, M. (2010). *Human stress ontology: Multiple applications and implications of an ontology framework in the mental health domain.* Paper presented at the 3rd International Conference on Health Informatics, Valencia, Spain.