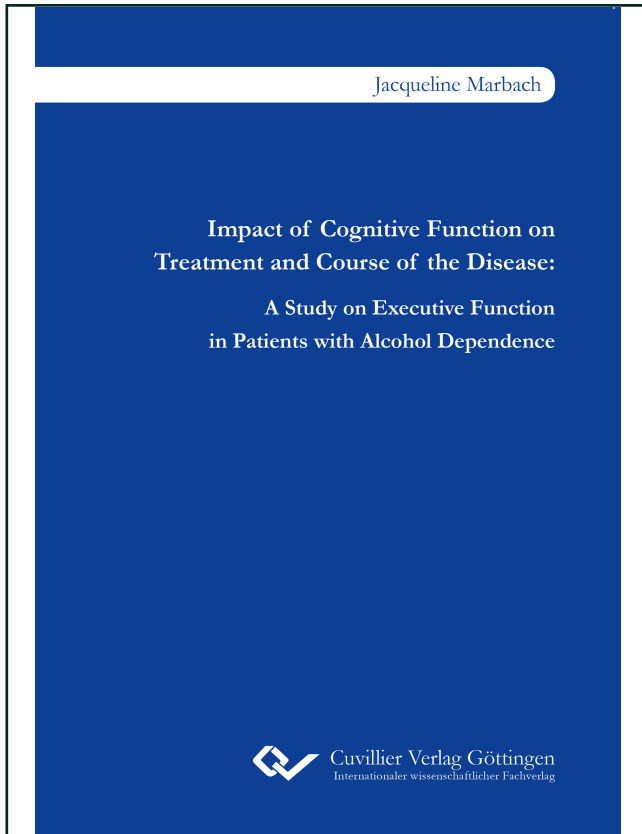




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Impact of Cognitive Function on Treatment and Course of the Disease

A Study on Executive Function in Patients with Alcohol Dependence



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Chapter 1: Introduction

Alcohol dependence is a disorder characterised by a strong desire for alcoholic drinks and loss of control over alcohol use, despite negative consequences in terms of physical health, and for personal, social and occupational functioning. There is a consistent body of research which indicates that excessive and chronic use of alcohol induces structural and functional abnormalities in the brain, and that this type of use is also associated with cognitive and behavioural deficits, including impairment in higher-order aspects of cognitive processes— namely executive functioning (Fama & Sullivan, 2014; Scheurich & Brokate, 2009; Parsons, 1998; Stavro, Pelletier, & Potvin, 2013).

Executive function is described as a product of co-ordinated operation of several processes to achieve a specific goal in a flexible manner (Funahashi, 2001). This flexible co-orientation of processes to accomplish a target-oriented action is provided by executive control systems. When these systems fail, behaviour becomes unregulated. Therefore, coordination, control and goal orientation are the most fundamental components in the concept of executive function (Elliot, 2003). In this regard, the prefrontal cortex (PFC) has been considered an important structure for executive control (Goldberg, 2001; Thier, 2002). Moreover, theoretical and empirical literature suggest that executive functions can be conceptualised according to two comprehensive domains (see Peterson & Welsh, 2014; Ardila, 2013): “cool” versus “hot” executive functions. “Cool executive functions” are defined as metacognitive skills which are important for goal-directed behaviour. These skills are involved in the processing of relatively abstract, context-free and non-emotional information. In contrast, “hot executive functions” are related to coordinating and controlling emotional behaviour (see Zelazo & Mueller, 2011; Zelazo, Qu & Mueller, 2005). Thus, the integration of metacognitive processes and affective processing are assumed to play an important role in guiding appropriate decision-making.

Unfortunately, there is no universal definition of executive function. Concerning this matter, researchers and clinicians have described various fundamental features of executive function, such as cognitive flexibility, impulse control, planning and problem solving, and working memory (Chung, Weyandt & Swentosky, 2014; Roth, Isquith & Gioia, 2005; Funahashi, 2001; Rende, 2000).

In general, the assessment of executive function is most challenging due to the fact that there is no test measure or battery that has been exclusively developed to explore executive dysfunctions. Processes of executive function are predominantly operationalised by psychometrical testing, and in some cases findings rely on questionnaires which are designed to capture real-world behavioural manifestations of executive function (Gioia & Isquith, 2004; Isquith, Roth, & Gioia, 2013).

In the field of alcoholism deficits are well documented in several features of executive functioning. Alcohol abuse disrupts important executive control processes which may make maintaining abstinence more difficult and could lead to a reinforcing cycle of craving and relapse (Bernardin, Maheut-Bosser, & Paille, 2014; Noel, Brevers, & Bechara, 2013).

The main issue discussed in this thesis is the impact of executive function deficits in the treatment and course of the disease. The main strength of this thesis is the attempt to evaluate the comprehensiveness and complexity of executive function by incorporating psychometrical and behavioural definitions. This methodological approach may help to identify the validity of cognitive and behavioural aspects of



executive functioning on the process of rehabilitation and daily functioning in patients with alcohol dependence. In other words, these different aspects of the same underlying construct are argued to influence addictive behaviour and the accomplishment of everyday demands, which are related to social and occupational functioning.



Chapter 2: Theoretical Approach

2.1 Alcohol Use Disorder

2.1.1 Definitions and Diagnostic Criteria

The first attempt to describe a concept of alcoholism was Jellinek's classification of the term into five types of conditions based on various drinking styles of individuals (Jellinek, 1960). Years later Edwards and Gross (Edwards & Gross, 1976) outlined a provisional description of a clinical syndrome that comprises the following essential elements: "a narrowing in the repertoire of drinking behaviours; salience of drink-seeking behaviour; increased tolerance to alcohol; repeated withdrawal symptoms; repeated relief or avoidance of withdrawal symptoms by further drinking; subjective awareness of a compulsion to drink, reinstatement of the syndrome after abstinence (p. 1058)".

As internationally established diagnostic methods, the *International Classification of Mental and Behavioural Disorders* (10th ed.; World Health Organization, 1992) and *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 2000) provide a standardised and systematic approach by allocating symptoms to diagnostic categories of alcohol-related disorders, such as "abusive use" and "dependence syndrome". While substance abuse causes various noxious effects, dependence syndrome is manifested by alterations at the psychological, biological and behavioural level (see Soyka, 1999). Even though the definitions of alcohol abuse and alcohol dependence are different, it is important to note that many effects caused by abusive drinking is also experienced by alcohol-dependent individuals; furthermore, the risk of developing addictive behaviour is increased by continued abuse.

The ICD-10 basic criteria for alcohol dependence and alcohol abuse are the same as those for substance dependence and substance abuse. The dependence syndrome is "a cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value".

A distinct diagnosis of substance dependence is made only if three or more of the following criteria have been present at the same time during the previous year:

1. a strong desire or sense of compulsion to take the substance;
2. difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use;
3. a physiological withdrawal state when substance use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
4. evidence of tolerance, such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses;
5. progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects;
6. persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy



substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

The DSM-IV describes substance dependence in much the same way as the ICD-10 does. Dependence syndrome is characterised by continued drinking despite recognition of physiological consequences related to alcohol, such as tolerance and withdrawal symptoms. Moreover, personal, work, and social relationships or responsibilities are abandoned or reduced because of substance use. The manual also describes the difficulty controlling the typically strong desire for alcohol use despite knowledge of harmful and persisting consequences.

There is some controversy as to whether definitions of alcohol use disorders should remain strictly categorical or if it should be conceptualised as a dimensional component (Helzer et al., 2006). The latest version of the DSM – DSM-5 (American Psychiatric Association, 2013) – combines the DSM-IV categories of substance abuse and substance dependence into a single disorder measured on a continuum from mild to severe. Furthermore, a variety of studies employing different statistical methods consistently propose as many as four homogeneous types of individuals with alcohol dependence: a chronic/severe type, a depressed/anxious type, a mildly affected type and an antisocial type (Hesselbrock & Hesselbrock, 2006).

Besides verifying the diagnosis of alcohol dependence it is important to assess addictive behaviour by determining the frequency and quantity of alcohol intake. In consideration of alcohol-related consequences, patients must be examined according to somatic disorders and psychosocial problems (see Lieber, 1995; Soyka, 1999; Gifford, 2010).

The ICD-10 diagnostic guidelines for alcohol dependence suggest that the “identification of the psychoactive substance should be based on as many sources of information as possible. These include self-report data, analysis of blood and other body fluids, characteristic physical and psychological symptoms, clinical signs and behaviour and other evidence such as a drug being in the patient’s possession or reports from informed third parties.” In the case of self-reported drinking behaviour, it is common that frequency and quantity of alcohol intake are trivialised (Schneider, 1999). Further, patients often dissimulate consequences that are at least partially attributable to abusive drinking, with regard to personal, social, work and financial situation.

2.1.2 Theoretical Approaches to Alcoholism

The current understanding of addiction is based on biopsychosocial principles. Addiction has been proposed to be a medical disease determined by: 1) *biological factors*, mostly genetic predispositions; 2) *psychological factors*, mainly the pursuit of pleasurable feelings, enhancement of performance, and suppression (self-medication) of psychiatric conditions such as anxiety, depression and other syndromes; and 3) *social-environmental factors*, the microenvironments and subcultures in which individuals live. The interaction of these factors facilitate the vulnerability to substance use disorders. Addiction is seen as a hijacking of the dopaminergic rewarding and reinforcing pathways of the brain while it weakens executive control functions related to the frontal lobes. The drug abusing individual continuously loses control



over drug intake. Basically, anatomical structures --such as the hippocampus (memory), the limbic system (emotion), and frontal lobe structures, especially the orbitofrontal cortex (motivation) -- play prominent roles in addiction. These hijacked reward pathways may influence processing in memory, emotion and motivation, and thus dominate the addicted individuals' behaviour. Finally, as addiction progresses, the dopaminergic reward pathways become less important, and the more complex anti-reward pathways begin to predominate. Eventually, addicted individuals continue the use of drugs to experience relief from pain and unpleasant feelings, which represents the dark side of addiction (see Levounis, 2015; Skewes & Gonzalez, 2013; Koob & Le Moal, 2008).

Noel, Brevers, et al. (2013) illustrated a neurocognitive approach to understanding the mechanisms of addiction. They proposed that addictive behaviour results from a conflict between two qualitatively different cognitive systems: an impulsive system and a reflective system (see also Bernardin et al., 2014). The *impulsive system* is a “bottom-up” system, where implicit cognitive processes are engaged in automatic and habitual behaviour via strong associative memory between addiction-related cues, outcome, and behaviours. The incentive effects between cues related to addiction (e.g. odours, places of consumption, or alcohol-related advertisements) and addictive behaviour is therefore underpinned by the impulsive system, which activates the dopaminergic system of the amygdala-striatal circuit. By contrast, the *reflective system* is a “top-down” system; it refers to controlled cognitive processes which enable appropriate behaviour. As a matter of fact, the impulsive system is regulated by executive control processes, and the reflective system depends mainly on prefrontal structures. Finally, an insula mediated neural system translates unconscious (or bottom-up) interoceptive signals (or somatic states) into conscious subjective experiences (e.g. desire or need) in order to guide decision making. In addiction this system plays a conflict management role between an addiction-related cue and a potentially associated somatic state - for example while experiencing withdrawal symptoms. It does this by reinforcing the activity of the impulsive system, and weakening the controlled (or goal-driven) cognitive processes needed for orderly processing of the reflective system. The imbalance between the impulsive system (i.e. automatic impulses) and reflective system (i.e. long-term goals) has been illustrated in alcoholism as a loss of willpower (Bechara, Noel, & Crone, 2006). In line with this neurocognitive approach, abusive alcohol use disrupts important executive control processes in the reflective system. When these executive functions are compromised, drinking behaviour gets out of control and is guided more strongly by automatic impulses (or implicit alcohol-related cognition). More precisely, impairment of inhibitory control and working memory capacity – the ability to maintain and manipulate goal-relevant information – are responsible for this dysregulation of the impulsive system by the reflective system (Houben, Wiers, & Jansen, 2011; Noel, Brevers, et al., 2013; Thush et al., 2008; Noel, Van der Linden, et al., 2007). Eventually, enhanced activation of the impulsive system causes sustained alcohol use and maintains addictive behaviour.

2.2 Neuropathology of Alcoholism: Changes in the Brain and Behaviour

This chapter will illustrate the scientific knowledge concerning neurochemical, structural and functional consequences in the brain following alcohol abuse. Its main focus will be the documentation of alcohol-induced cognitive dysfunction. Particularly interesting, it will also illuminate the effects of abstinence, withdrawal and relapse on cognitive functions. Overall, the question arises why people keep drinking in spite of serious negative outcomes related to alcohol abuse. The field of addiction research offers many answers to that question.



2.2.1 The Role of Neurotransmitters

Alcohol interacts with several neurochemical mechanisms; especially, in specific brain reward and stress circuits (Koob, 2003). These interactions result in alcohol's acute reinforcing effects. Chronic exposure to alcohol interrupts the regular functioning of neurotransmitters that underlie the development of alcoholism (Banerjee, 2014; Mukherjee, Das, Vaidyanathan, & Vasudevan, 2008).

In the following section some of the neural circuits relevant in alcoholism are illustrated, categorised by neurotransmitter systems, i.e. GABAergic, glutamatergic, dopaminergic and serotonergic neural circuits (Banerjee, 2014; Ratsma, Van Der Stelt, & Gunning, 2002).

Both acute and chronic alcohol intake alter the inhibitory neurotransmitter GABA and the excitatory neurotransmitters glutamate, dopamine and serotonin. These alterations may account for the reinforcing and rewarding effects of alcohol, and for alcohol withdrawal symptoms (Wong, Maini, Rousset, & Brasic, 2003).

In line with a review by Valenzuela (1997) alcohol intake affects the brain chemistry by disrupting the balance between inhibitory and excitatory neurotransmitters. Short-term alcohol exposure depresses brain function by altering the balance between inhibitory and excitatory neurotransmission in favour of inhibitory influences. The major inhibitory neurochemical marker in the brain is GABA. GABA generates a state of sedation and decrease in anxiety by reducing excitatory neurotransmission. Amino acids aspartate and glutamate are crucial excitatory neurotransmitters. With long-term alcohol consumption, alcohol forces the brain to compensate, or rather it attempts to restore balance by decreasing the inhibitory neurotransmission (i.e. GABA receptor function) and increasing the excitatory neurotransmission. These neurochemical compensatory processes may be involved in the development of tolerance to alcohol's effects. When alcohol consumption is reduced or ceased abruptly after long-term use a withdrawal syndrome can occur. The withdrawal syndrome is neurobiologically supported by the imbalance between GABA and glutamate-NMDA neurotransmission (Rolland, Karila, Guardia, & Cottencin, 2011), where increases in glutamate release are observed during the initial stages of withdrawal from chronic alcoholism due to alterations in the sensitivities of the NMDA receptors (Ward, Lallemand, & de Witte, 2009). Further, these changes in the neurochemistry induce craving and maintain the alcohol-seeking behaviour (Valenzuela, 1997).

Furthermore, dopamine production is increased by alcohol intake, generating euphoric feelings (Gifford, 2010). Dopaminergic mechanisms seem to be involved in the rewarding effects of alcohol via activation of positive reinforcement and thereby influences the development and relapse of alcohol dependence (Banerjee, 2014; Mukherjee et al., 2008). The serotonergic system, however, mediates negative reinforcement (Mukherjee et al., 2008). Dysfunction of serotonergic neurotransmission has been reported to be associated with a different behaviour pattern, specific to alcoholism; namely impulsive aggression, negative mood states, and excessive alcohol intake (Heinz, Mann, Weinberger, & Goldman, 2001; Moeller & Dougherty, 2001).

In terms of stress circuits, GABAergic neurotransmission is presumably important in addiction-associated stress because GABA modulates emotion and response to stress (Enoch, 2008). In contrast to glutamate, GABA inhibits the hypothalamic-pituitary-adrenal axis (HPA) responses to stress (Herman, Mueller, & Figueiredo, 2004). Stress exposure immediately reduces GABA-stimulated chloride influx in the frontal cortex and amygdala (Martijena, Rodriguez Manzanares, Lacerra, & Molina, 2002). In a review,



Mody and Maguire (2011) illustrated a reciprocal regulation of stress hormones and GABA receptors. GABAergic transmission is relevant in the regulation of the HPA axis and the production of stress hormones, besides stress-derived neurosteroids can alter GABA(A) receptor subunit expression and directly modulate GABAergic transmission. Further, corticotropin-releasing factor (CRF) and GABAergic systems in the central amygdala (CeA) are associated with the high-anxiety, high-drinking profile related to alcohol dependence. These findings indicate that specific presynaptic CRF-GABA interactions in CeA play a key role in the development and maintenance of alcohol dependence (Roberto et al., 2010).

Begleiter and Porjesz (1999) hypothesise that individuals with a genetic predisposition of developing alcoholism demonstrate a homeostatic imbalance between excitatory and inhibitory neural mechanisms. This imbalance of the central nervous system (CNS) is similar to the state of hyperexcitability or CNS disinhibition, respectively, which may enhance the response to alcohol. Individuals with a high risk of developing alcoholism are speculated to be more sensitive to the reinforcing effects of alcohol and less sensitive to the detrimental effects of alcohol.

2.2.2 Brain Structure and Function Involved in Alcohol Use

Due to the fact that alcohol is a small molecule dissolvable in both water and lipids, investigators have postulated that alcohol pervades all tissues of the body and impairs most vital functions (Lieber, 1995). Therefore, alcohol use can cause structural and functional abnormalities in the brain (Buhler & Mann, 2011; Harper, 2007) and other organs, and as a result causes cancer (Boffetta & Hashibe, 2006; Druesne-Pecollo et al., 2009; Testino, 2011), liver disease (Addolorato et al., 2009; Gleeson et al., 2009; Smith et al., 2006) and heart disease (Rehm, Gmel, Sempos, & Trevisan, 2003; Ren & Wold, 2008).

With the discovery that there is increasing damage to the brain from moderate social drinking to chronic excessive alcohol consumption – inducing cognitive deficits from mild, to moderate, to severe deficits, similar to those seen in brain-damaged individuals (Parsons, 1998) – intensive research has been made to the scientific and clinical understanding of alcoholism.

Drawing on the literature, there are mainly three hypotheses concerning brain regions involved in alcoholism (see Ratti, Bo, Giardini, & Soragna, 2002):

- I. “Right-hemisphere hypothesis”: The right-hemisphere functions are more severely impaired than left-hemisphere functions (Ellis & Oscar-Berman, 1989; Nicolas et al., 1993; Beatty, Hames, Blanco, Nixon, & Tivis, 1996).
- II. “Global brain damage hypothesis” or “diffuse brain deficit hypothesis” or “premature aging hypothesis”: Impairment of cognitive functions are related to both right- and left-hemispheres, whereas the pattern of cognitive deficit in individuals with alcohol dependence are similar to those seen in older individuals (Parsons, 1998; Ryan & Butters, 1980).
- III. “Anterior brain deficit hypothesis”: The cognitive functions related to the frontal lobe are basically impaired in individuals with alcohol dependence (Adams et al., 1993; Giancola & Moss, 1998; Tuck & Jackson, 1991).



In the following sections, alcohol-related cognitive, behavioural, and emotional impairments will be illustrated. These impairments are linked to abnormalities in brain regions, whereas the frontal lobe structures, limbic system, and cerebellum are most susceptible to damage and dysfunction (Oscar-Berman & Marinkovic, 2007a; Oscar-Berman & Marinkovic, 2007b; Ratti et al., 2002; Kopera et al., 2012; Loeber et al., 2009; Moselhy, Georgiou, & Kahn, 2001; Noel, Bechara, Dan, Hanak, & Verbanck, 2007; Zinn, Stein, & Swartzwelder, 2004; De Bellis et al., 2005; Pfefferbaum, Sullivan, Mathalon, & Lim, 1997). Furthermore, structural changes observed in alcoholism include reduced thickness of the corpus callosum (Buhler & Mann, 2011; Kril, Halliday, Svoboda, & Cartwright, 1997; Schulte, Pfefferbaum, & Sullivan, 2004) and enlargement of ventricles (Kajander et al., 2001; Kril & Halliday, 1999; Rosenbloom et al., 2007).

2.2.2.1 The Frontal Lobes

The frontal lobes are anatomically connected to all other lobes of the brain. They also receive and send fibres to numerous subcortical structures (Fuster, 1997). While posterior regions of the frontal lobe are responsible for motor control, the anterior region, namely the prefrontal cortex (PFC), is crucial for executive control functions in the brain (Goldberg, 2001; Thier, 2002). Executive functions are described as integrated cognitive processes that determine goal-directed behaviour and are fundamental in the orderly execution of daily life activities. These activities include the ability to formulate goals, initiate behaviour, anticipate the consequences of actions, plan and organise behaviour, and monitor and adapt behaviour (Cicerone et al., 2000). Different areas of the PFC are interconnected with other brain areas processing external information of sensory modalities and cortical and subcortical motor system structures as well as internal information from limbic and midbrain structures, which play a central role in emotion, memory, and reward. In short, the neuronal activity in PFC enables information about the external and internal world to be processed in order to produce goal-directed behaviour (Miller & Wallis, 2009).

The key problem in addiction is the inability to stop substance use despite knowing about harmful and persisting consequences. A decrease in the frontal cortical thickness may be responsible for maladaptive behaviours or continuation of abusive substance use; this then activates a neurotoxic effect on frontal cortical tissue (Fortier et al., 2011). The frontal-cortical areas of the brain monitor behavioural control through executive functions. PFC, anterior cingulate cortex (ACC, a part of the limbic system) and orbitofrontal cortex (OFC, a major region of the PFC) contribute to executive functions; particularly reflection, attentional gating, emotional processing and inhibition of impulses (Crews & Boettiger, 2009; Perry et al., 2011). Thus, damage to specific cortical structures due to alcohol and substance abuse may cause impulsiveness from the dysfunction of frontal-cortical inhibitory control of impulses and increased limbic-driven impulsive system (Crews & Boettiger, 2009). While impulsivity is discussed as a consequence of substance use, Cadet and Bisagno (2013) state that individuals addicted to drugs seem to be narrowed in their scope of goals. The substances of abuse seem to become more salient than other choices in daily life. This narrowing might depend on abnormal dynamics of dopamine release in the PFC with subsequent effects on corticostriatal glutamate projections to the dorsal striatum that might be associated with compulsive manifestations of addictive behaviour.

Furthermore, neuroimaging techniques provide evidence of the activity in the OFC and its connections with the subcortical associative learning nodes, such as basolateral amygdala and nucleus accumbens.



Due to these connections, the OFC is uniquely positioned to activate associative information to guide decisions in the future. Substance-induced alterations in these neural circuits might account for the maladaptive behaviour; including expectancy, craving and deficits in decision making seen in substance use disorders (London, Ernst, Grant, Bonson, & Weinstein, 2000; Schoenbaum, Roesch, & Stalnaker, 2006).

Specific to alcoholism, several studies have reported widespread alcohol-induced reduction, particularly in frontal brain regions (Fortier et al., 2011; Moselhy et al., 2001; Ratti et al., 2002). Neuronal loss has been documented in the frontal association cortex in patients with alcohol dependence (Harper, 1998). Pfefferbaum et al. (1997) found alcohol-induced volume loss in the frontal lobe using MRI. There is considerable evidence that alcohol-dependent patients with and without Korsakoff's Syndrome (KS) show grey and white matter abnormalities. The damage is principally observed in the prefrontal cortex, and the degree of the damage generally is more severe in KS patients (Oscar-Berman, 2012). Volkow et al. (2008) illustrated that acute alcohol administration significantly increases cerebral blood flow (CBF) in several brain regions including the PFC; there the increases are linked to alcohol's reinforcing effects.

2.2.2.2 The Cerebellum

The cerebellum plays an important role in motor control and motor learning. Damage to the cerebellum results in loss of coordination, namely ataxie, and dysfunction in motor learning (Timmann, 2012). Neuroimaging findings demonstrate that the cerebellum processes information to various nonmotor areas of the cerebral cortex. Cerebellar input and output nuclei are connected with areas in the prefrontal, parietal and sensory cortex, as well as motor and premotor cortex. The range of functions related to activation in the cerebellum is substantial and includes attention, executive control, language, working memory, learning, pain, emotion, and addictive behaviour (Strick, Dum, & Fiez, 2009; O'Reilly, Beckmann, Tomassini, Ramnani, & Johansen-Berg, 2010; Timmann, 2012). Diseases confined to the cerebellum are associated with a specific pattern of clinically relevant cognitive and behavioural deficits, termed as the "cerebellar cognitive affective syndrome" (CCAS), including decline in executive functioning such as planning, set-shifting, verbal fluency, abstract reasoning and working memory; difficulties with visual-spatial skills; language deficits and altered personality with blunting of affect or disinhibited and inappropriate behaviour (Schmahmann & Sherman, 1998).

Cerebellar degeneration is frequently observed in chronic alcohol abuse and is characterised by ataxia of stance and gait (Sullivan, 2003; Andersen, 2004). Cerebellar vermis white matter volume was shown to be reduced in ataxic alcohol-dependent patients by 42% (Baker, Harding, Halliday, Kril, & Harper, 1999).

Due to associations with the frontal lobe a functional role for fronto-cerebellar circuitry is proposed (Schmahmann, 1997). In a review, Zahr, Pitel, Chanraud, and Sullivan (2010) summarised that disruption of fronto-cerebellar circuitry is one of the major neural mechanisms underlying behavioural deficits in both uncomplicated alcoholism and alcohol-dependent individuals with neurological pathologies such as Wernicke- Korsakoff-Syndrom (see also Wijnia & Goossensen, 2010), resulting in alcohol-related cognitive and motor impairment. Even moderate alterations within this fronto-cerebellar circuitry in patients with alcohol dependence can account for relapse due to deficits in frontal lobe "executive" functioning. Further findings have reported changes to the main nodes and connections of the fronto-cerebellar circuitry connecting the frontal cortex to the thalamus and cerebellum via the ventral pons



(Pitel et al., 2009; Sullivan, 2003; Sullivan et al., 2003). Chanraud et al. (2007) found decreases in gray matter volume in the frontal lobe, cerebellum, thalamus, insula and hippocampus, and white matter decrease in the brainstem (pons) in alcohol-dependent individuals. They suggested that frontal reductions of brain volume and alterations within cerebello-thalamo-cortical circuits may initiate degradation of executive functioning.

Furthermore, Fitzpatrick, Jackson, and Crowe (2008) suggest that a subgroup of alcohol-dependent patients with alcoholic cerebellar degeneration also may contribute for higher-order cognitive and affective deficits, as described in CCAS.

2.2.2.3 The Limbic System

The limbic system is responsible for learning and memory functions. Additionally, it plays a prominent role in the generation, integration and control of emotional processes while connecting them with behavioural responses. For example, the appraisal of a dangerous situation and the decision to respond appropriately (fight-or-flight response), implies several limbic brain structures (Braun, 2011). Principal areas of the limbic system include the hippocampus, amygdala, hypothalamus, and anterior cingulate gyrus (Oscar-Berman & Marinkovic, 2007a). Braun (2011) illustrated that the regions that form the limbic system include subcortical regions (i.e. hypothalamus, amygdala, mammillary bodies, nucleus accumbens, septum, and thalamic nuclei) and cortical regions (i.e. hippocampal formation, insular cortex, OFC, cingulate gyrus, and parahippocampal gyrus). Further, the limbic system is closely linked to the autonomic nervous system through which endocrine functions (i.e. hormonal responses during stress) are regulated via the hypothalamus. Alterations in areas such as the hippocampus, amygdala and medial prefrontal cortex are responsible for hypothalamic-pituitary-adrenal (HPA) axis dysfunction and may be responsible for the etiology of affective disorders (Herman, Ostrander, Mueller, & Figueiredo, 2005) and attention deficit-hyperactivity disorder (Bush, 2011).

It is therefore likely that the limbic structures may be sensitive to the toxic effects of alcohol. Alcohol strongly affects inhibitory transmission in the central amygdala (Roberto, Gilpin, & Siggins, 2012). Another study suggested a relationship between amygdala volume reduction, craving and potential relapse into alcohol consumption (Wrase et al., 2008). Other findings proposed a reduction of hippocampal volume in alcohol-dependent individuals (De Bellis et al., 2000; Welch, Carson, & Lawrie, 2013; Kurth et al., 2004). Zuccoli et al. (2009) observed more frequent contrast enhancement in the mammillary bodies and thalamus in alcohol-dependent patients compared with patients that were not alcohol-dependent, suggesting that these areas may be especially sensitive to the toxic effects of alcohol.

Accumulating findings indicate that alcoholism leads to distinct damage to the Papez's circuit. This brain circuitry is particularly involved in episodic memory and includes the hippocampus-anterior-thalamus axis, even though episodic memory functioning also relies on internal temporal and frontal cortices (Beaunieux, Eustache, & Pitel, 2015). Hence, degradation of limbic structures combined with atrophy of frontal lobe areas is important in alcoholism (Savage, 2015). In patients with alcoholic Korsakoff's syndrome (KS) brain damage involves considerable frontal and limbic circuitries as well as the well-established impairment in mnemonic abilities related to thalamic structures and medial temporal lobe regions. Frontal and limbic abnormalities include confabulation (distortions regarding episodic/autobiographical memory domain), impairment in cognitive control (action decision, impulse



control), and emotional dysregulation (emotional flatness, apathy) (Oscar-Berman, 2012; Moselhy et al., 2001; Pitel et al., 2009).

2.2.2.4 Corpus Callosum

The corpus callosum connects the left and right cerebral hemispheres and represents the cardinal fibre pathway in the brain; it provides means for efficient interhemispheric information processing (Kolb & Whishaw, 1996). Structural changes of the corpus callosum may reduce parallel information processing. Schulte et al. (2004) proposed that chronic alcohol use together with older age induce disruption on parallel interhemispheric processing reliant on callosal connections. Alcohol-induced degeneration of the corpus callosum is stated to be associated with impairments in visual and logical memory, visuospatial ability as well as working memory and cognitive flexibility (Estruch et al., 1997; Pfefferbaum, Adalsteinsson, & Sullivan, 2006).

2.2.3 Alcohol-Related Cognitive Dysfunctions

There is little doubt that excessive and chronic alcohol use affects cognition and behaviour, including deficits in basal and higher-order aspects of cognitive functioning. Neuropsychological data have linked it with a decline across multiple cognitive domains, such as attentional performance and psychomotor processing, learning and memory, visuospatial skills, motor demands and executive functioning (Scheurich & Brokate, 2009; Parsons, 1998; Stavro et al., 2013).

Alcohol-related cognitive dysfunction is not described as a general decline in all cognitive domains. Rather it is associated with a particular pattern of deficits in cognitive functions. However, it is difficult to specify the pattern and severity of compromised cognitive functions due to the differing effect of age, alcohol intake, gender, comorbid medical and psychiatric conditions, and dissimilar demographics among individuals (Fama & Sullivan, 2014).

In the following sections there will be given a brief overview according to cognitive domains mainly affected by alcoholism (see Fama & Sullivan, 2014; Scheurich & Brokate 2009).

2.2.3.1 Attentional and Psychomotor Performance

A study examining attention processes by using a computer-assisted method revealed that patients with alcohol dependence performed as well as controls on subtests regarding alertness, selective and divided attention (Loose et al., 2001). Further, no decline was found in sustained attention (Kathmann, Wagner, Satzger, & Engel, 1996). However, alcohol-dependent participants demonstrated considerable difficulties when tasks required more complex attentional processes, particularly with regard to executive demand, such as attentional processing in working memory (Ambrose, Bowden, & Whelan, 2001) and inhibitory control (Bardenhagen, Oscar-Berman, & Bowden, 2007; Brokate, Bernsdorff, Braamhorst, Eling, & Hildebrandt, 2008; Naim-Feil, Fitzgerald, Bradshaw, Lubman, & Sheppard, 2014).