processes. The first - necrosis - follows a complete overwhelming of the homeostatic processes in the cell and is associated with swelling and then disruption of the nuclear endoplasmic reticular and cell surface membranes. The cell splits open, spilling its contents into the extracellular space. The second cell death process is called apoptosis which is an active suicide in which the cell uses its own cellular mechanisms to initiate a series of molecular events that lead to the cell digesting away many of its components from the inside (Fawcett et al., 2001). These two processes are depicted diagrammatically in Figure 2.1 below.

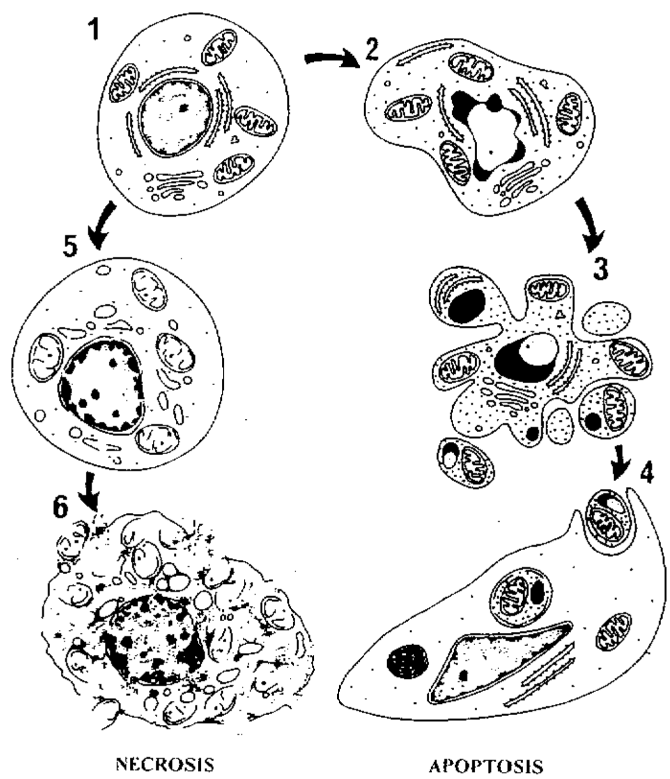


Figure 2.1: The appearance of necrosis and apoptosis (Fawcett, Rosser & Dunnett, 2001)

2.3 MECHANISMS OF RECOVERY IN STROKE

Recovery can be divided roughly into two stages. During first stage recovery the acute effects of metabolic and membrane failure, ionic and transmitter imbalance, haemorrhage, cellular reaction and oedema need to be stabilised. The re-establishment of circulation in areas of partial ischemia or ischemic penumbra and reperfusion after thrombolysis are possible early mechanisms of recovery (Wise, 2003). Damage can be reversed if blood flow can be elevated beyond anoxic values and many of the neuroprotective agents try minimising damage by protecting cells in the penumbra until oxygenation can be restored. The first few days and aphasia (Kertesz, 2007). Anomic aphasia is also often observed (Alexander & Loverme, 1980). Lesions in the putamen and anterior internal capsule produce slow, anomic, dysarthric speech and with posterior extension, comprehension can also be impaired with paraphasic speech and jargon (Damasio, Damais, Rizzo, Varney & Gersh, 1982).

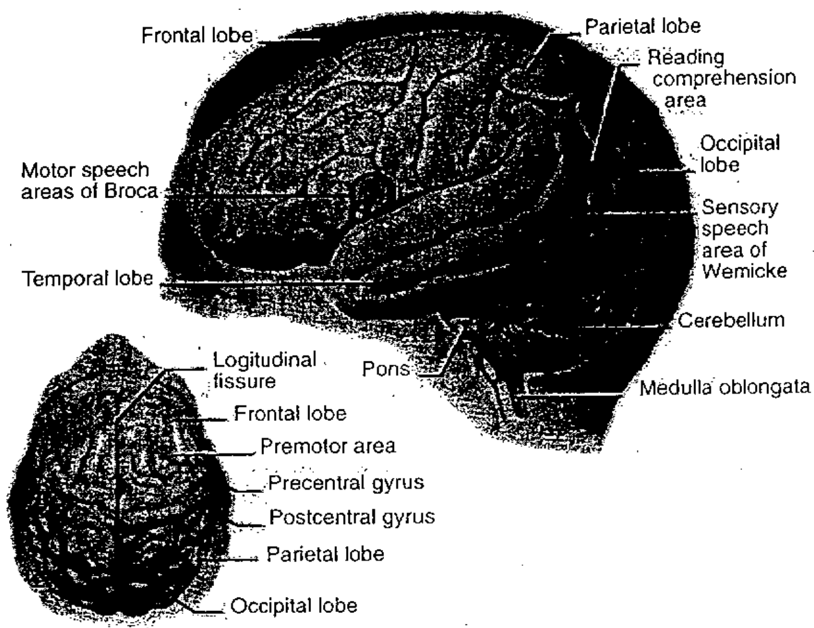
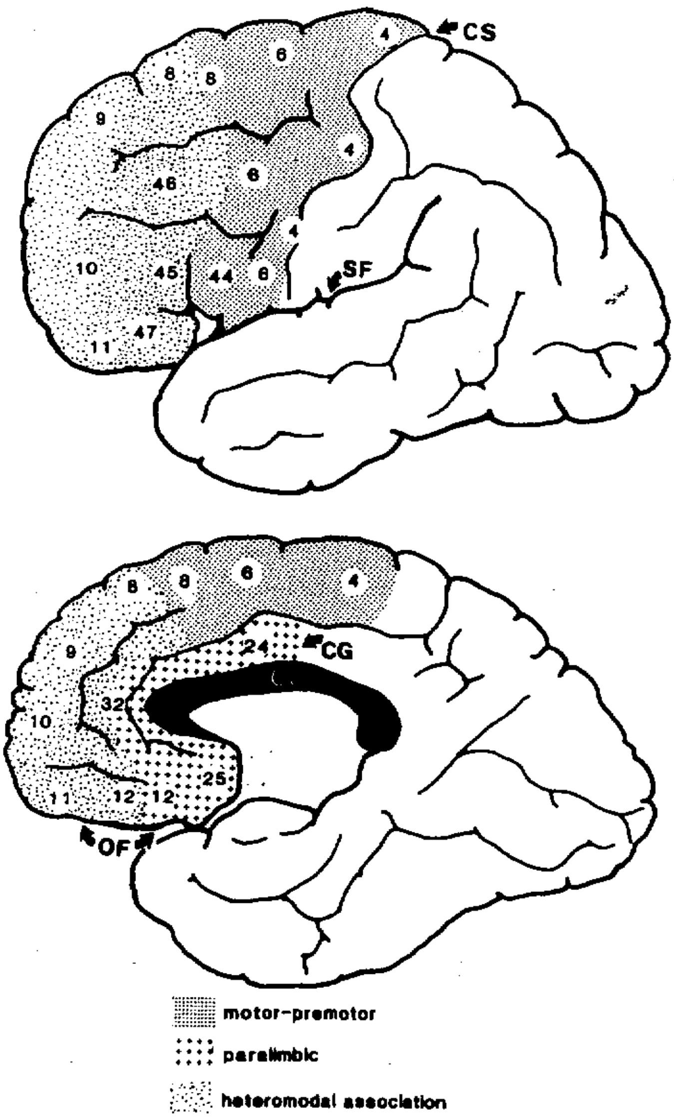


Figure 2.2: Major lobes of the brain with location of important language areas.

In addition to the aphasia syndromes that result from stroke, there are a number of acquired dyslexias (reading disorders) as well as agraphias (writing disorders) that are associated with aphasia. Three major psycholinguistic classifications of reading disorders have been identified: deep dyslexia, surface dyslexia and phonologic alexia (Webb, 2005). In deep dyslexia, there is a disruption of semantic representations and impaired grapheme-to-phoneme conversion. Therefore, errors are semantically related to the target, the patient can not read pseudowords, there is little effect of length or spelling regularity but a pronounced effect of frequency (Webb, 2005). In surface dyslexia, the impairment rests in an inability to access the grapheme input lexicon or the representations within. Errors are phonologically related to the target and there is a pronounced effect of spelling regularity (Webb, 2005). Phonologic alexia represents an impairment of grapheme-to-phone conversion and patients exhibit an inability to read pseudowords and difficulty with low frequency words (Webb, 2005).

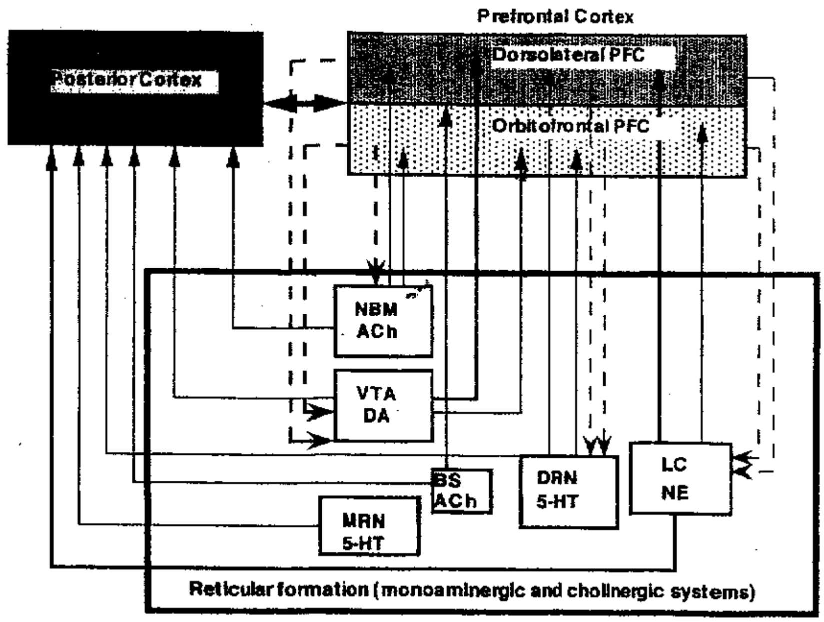
In a similar vein, McNeil and Tseng (2005) describe agraphia subtypes based on neuropsychological/psycholinguistic models. In lexical or surface agraphia, difficulty arises



Lateral (*top*) and medial (*bottom*) views of the frontal lobes. The numbers refer to the Brodmann nomenclature (Brodmann, 1909). CC, corpus callosum; CG, cingulate gyrus; CS, central sulcus; OF, orbitofrontal surface; SF, Sylvian fissure.

Figure 3.1: Lateral and medial views of the frontal lobes and prefrontal cortex (Mesulam, 2002)

First, sensory information in post-Rolandic areas is provided to the orbitofrontal cortical region. This area is extensively connected to the hypothalamus, amygdala, hippocampus and also the other paralimbic cortices in the temporal pole, insula, parahippocampal gyrus and cingulate gyrus (Mesulam, 2002). The significance of these connections is that they are thought to be critical for the regulation of emotional consequence and motivational value of stimuli. Second, the mid-ventrolateral prefrontal region via its strong bidirectional connections can exercise a top-down modulation of activity for the purpose of strategic judgment, encoding, and retrieval of information (Petrides & Pandya, 2002). Third, the dorsolateral prefrontal region is critical for monitoring of information in working memory, necessary for high level planning and manipulation of information. The interaction between the mid-dorsolateral prefrontal region and the memory system may be exercised via the dorsal limbic pathway that links reciprocally with the hippocampal system. The posterior dorsolateral frontal cortex appears to underlie



Schematic to show main anatomical connections between chemically defined ascending systems of the reticular core and the neocortex (posterior cortex and prefrontal cortex [PFC]; the latter is shown simplistically divided into the dorsolateral and orbitofrontal regions). Projections to the PFC are shown as solid lines; projections from the PFC are shown as dashed lines. The monoamines and acetylcholine (ACh) project to all sectors of the PFC, although there is some variation in the density of innervation for some areas (e.g., for the catecholamines dopamine [DA] and norepinephrine [NE]; see Lewis et al. 1988). There are some differences of innervation in comparison to the posterior neocortex—e.g., the relative lack of strong DA projections. Note also the feedback pathways from the PFC to the vicinity of the cell groups of origin of the ascending systems—e.g., the orbitofrontal cortex to the basal forebrain cholinergic cells (Mesulam, 1995), while the dorsolateral PFC projects to the locus coeruleus (LC) (Arnsten & Goldman-Rakic, 1984). This pattern of projections is intriguing given that the orbital PFC and basal forebrain cholinergic cells often fire on the basis of stimulus relationships to reward (e.g., Richardson & DeLong, 1986; Rolls, 1996), while the dorsolateral PFC and LC are more related to regulation of attention (e.g., Foote et al., 1980; Woods & Knight, 1986). Indeed, one of the special features of the PFC, perhaps unique among cortical areas, is its ability to regulate these chemical systems and thus alter modulation of most brain functions.

This figure is based in part on findings summarized in the following publications: Goldman-Rakic (1987); Lewis et al. (1988); Sesack et al. (1989); Lewis (1990); Williams and Goldman-Rakic (1998); Cavada et al. (2000); and Ongur and Price (2000); BS-ACh, brain stem cholinergic cell groups; DRN, dorsal raphe nuclei; MRN, median raphe nuclei; NBM, nucleus basalis of Meynert; VTA; ventral tegmental area; 5HT, 5-hydroxytrytamine (serotonin).

Figure 3.2: Neurochemical transmission in the PFC (Arnsten & Robbins, 2002)

3.3.3.1 Dopamine

Working memory is a critical component of EF and has significant impact on the ability of individuals to participate meaningfully in conversation. The two elements integral to working memory, sensory retrospective memory and sensory prospective memory, allow individuals to remember the past and engage in preparation to act, respectively (Fuster, 1995; Goldman-Rakic, 1995). People are able to construct hypotheses about how to act in the present and future based on previous experience, thus if one is unable to look back, one is unable to look forward, remaining instead in the dislocated present (Barkley, 1998). Therefore, patients with working memory deficits may display a tendency to be more influenced by context and external stimuli and less controlled by internally represented information, giving rise to a temporal myopia (Stuss & Benson, 1986). In conversation, this would result in impaired ability to maintain the thread of discourse, particularly in multi-party interactions, difficulty integrating new

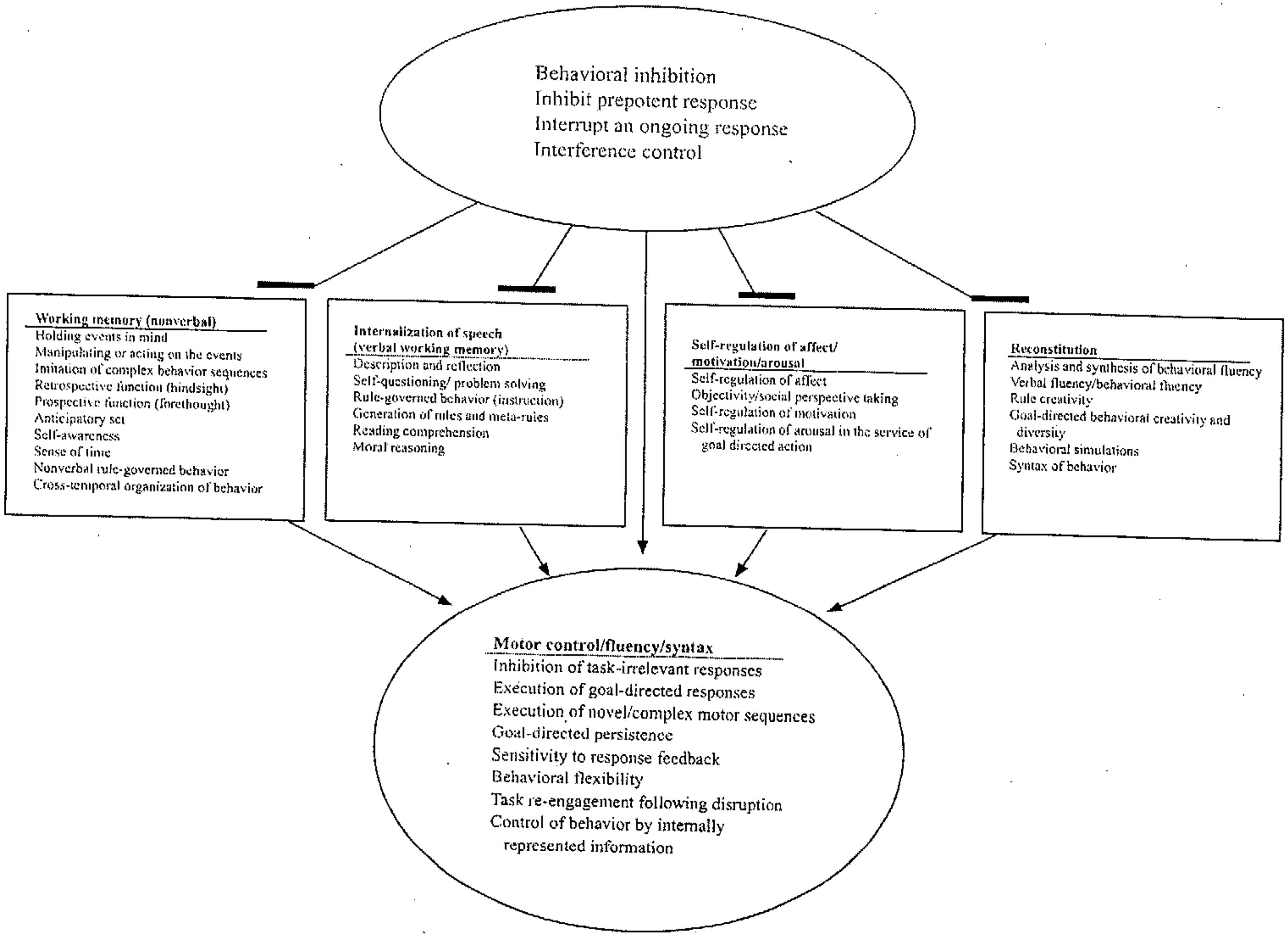
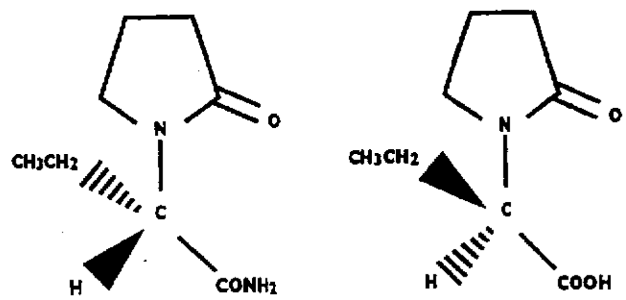


Figure 3.3. Barkley's model of behavioural inhibition and executive function (1997).

central nervous system (Genton & Van Vleyman, 2000). Figure 4.2 below depicts its chemical structure and its primary pharmacologically inactive metabolite LO57.



Levetiracetam L057

Figure 4.1: The chemical structure of LEV and its metabolite LO57.

LEV was initially evaluated in models of cognitive impairment with the primary objective of finding a drug more effective than the better known piracetam (Genton & Van Vleymen, 2000), which has a history of use in patients with aphasia (see discussion above). In preclinical efficacy trials, LEV has been found to improve learning and memory in animals with underlying cerebral ischemia (Gobert, Verloes & Gower, 1988 cited in Genton & Van Vleymen, 2000).

Despite early data that demonstrated that piracetam demonstrated greater and more consistent cognitive benefits than LEV (Genton & Van Vleymen, 2000), more recent studies have started looking at the influence of LEV on cognitive function. Loring and Meador (2004) listed improvements in cognition, concentration as well as increased alertness in children with epilepsy treated with LEV. These improvements occurred in several patients without improved seizure control. Frings, Quiske, Wagner, Carius, Homberg, and Schulze-Bonhage, (2003), demonstrated statistically significant improvements in selective attention, verbal working memory and verbal fluency as well as in a visual planning task in eighteen epileptic patients introduced to LEV. A case study published by Canevini, Chifari and Piazzini (2002), described the disappearance of stuttering behaviours and improvements in verbal fluency in a 34-year-old woman treated with LEV. They postulated that LEV might influence the metabolism of the language area thereby increasing verbal fluency. A particularly interesting case study was reported by Kossoff, Boatman and Freeman (2003). A 5-year-old with Landau-Kleffner

6.2.4 Results with reference to site of lesion

A growing body of neuro-physiological research using functional imaging techniques such as fMRI and PET scans has also contributed to the neurological sites implicated in performance of a variety of neuropsychological and executive tasks (Damasio & Anderson, 2003). Several strands of research have convincingly argued that cognitive control is not attributable to a single unitary system but rather emerges from the interaction of separable systems, which are responsible for complementary control functions (Gruber & Goschke, 2004). These systems include the prefrontal cortex, inferior parietal cortex and anterior cingulate cortex (Abutalebi & Green, 2007). The chief neural component is the prefrontal cortex which supports several classes of executive disorders, which have been differentiated roughly into behavioural and cognitive domains (Godefroy & Stuss, 2007). This distinction is compatible with two major functional/anatomical dissociations within the frontal lobes (Stuss & Levine, 2002). Cognitive aspects of EF are mainly supported by the circuit from the dorsolateral frontal cortex, involved primarily with spatial and conceptual reasoning and the behavioural component by the lateral orbital and medial frontal/anterior cingulated circuits involved in emotional processing. Exactly how these discrete regions and their differential connections contribute to the executive role of the prefrontal cortex remains to be delineated (Elliot, 2003). Figure 6.1 from Abutalebi and Green (2007) presents a schematic model of the areas involved in executive control.

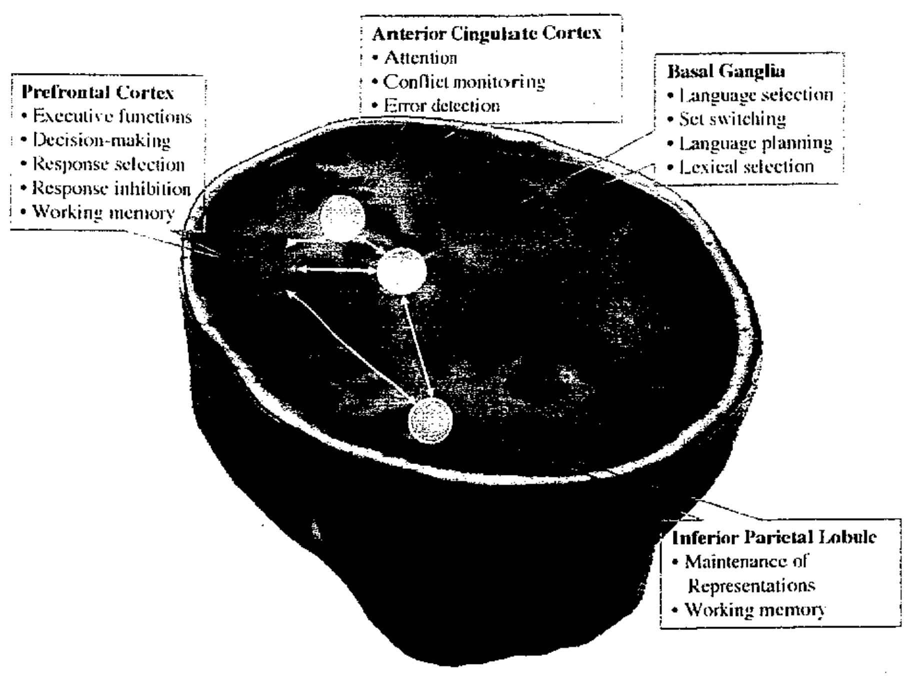


Figure 6.1 – Schematic representation of areas involved in cognitive control