CHAPTER 17

Hypnosis and Cingulate-Mediated Mechanisms of Analgesia

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Chapter contents

Throughout the history of hypnosis, speculation about the basic nature and underlying causes of these phenomena has been full of controversies, conflicts and passion. Theories of hypnosis are generally divided into psychological and physiological theories. The psychological theories of hypnosis emphasize role definition, expectation, and subject motivation, while physiological theories emphasize the neural bases of hypnosis. Currently, there is an agreement that, in addition to the changes in external behavior, suggestions presented in a hypnotic context may give rise to changes in subjective experience. The disagreement has focused on the question whether reference to a specific internal state of the individual called the hypnotic state is necessary to describe or explain the objective and subjective changes associated with hypnosis. While some researchers postulated an altered state of consciousness, others caution that the evidence only supports a state of high suggestibility. Subjects in hypnosis reported vivid images, hallucinations in all sense modalities, amnesia, timelessness, detachment from the self and willingness to accept distortions of logic and reality. They experience a lack of initiative or willful movement.

Hypnosis investigators have long sought specific physiological indicators of this state. Some of the first physiological responses to be studied were autonomic in nature such as heart rate, blood pressure, and galvanic skin responses (Jana, 1967; Tebecis & Provins, 1976; Ray *et al.*, 2000). Much of the early research in this area was fuelled by investigators seeking to confirm that the identification of a specific physiologic indicator of hypnosis would lend support to the view that hypnosis is a state of consciousness distinct from other states, such as normal wakefulness or sleep and cortical electroencephalographic activity during hypnosis was thought to be unlike cortical activity during sleep (Gorton, 1949). Until now, no physiological indicator has been identified that consistently shows characteristics unique to hypnosis. Electroencephalographic (EEG) studies (Sabourin *et al.*, 1990; Perlini & Spanos, 1991; Williams & Gruzelier, 2001; Croft *et al.*, 2002) and evoked potential studies (Barabasz *et al.*, 1999; Friederich *et al.*, 2001) failed to uncover an unambiguous physiological marker of hypnosis. In contrast, recent neuroimaging has demonstrated changes in neural activity that may provide critical markers of this state (Maquet *et al.*, 1999; Rainville *et al.*, 1999; Schulz-Stubner *et al.*, 2004). The cerebral activation pattern during hypnotic suggestion occurred predominantly in the occipital, parietal, temporal, ventrolateral prefrontal, and anterior cingulate cortices was widespread and depended upon the content of the hypnotic demand.

There are many case reports and studies that support the use of hypnosis for surgical analgesia. The most time honored of these are those of Esdaile, a Scottish surgeon, who reported on 345 major operations in the 19th century with hypnosis as the sole anesthetic and with extremely low mortality rates for the times (5% instead of 40%; see Forrest, 1999). Simultaneously with this success using hypnosis, ether and chloroform became popular and displaced the use of hypnosis for anesthesia in surgery.

As alternative treatments for medical conditions become popular, contemporary medicine is being challenged to take a more integrative approach and this includes hypnosis. Relevant clinical trials involving hypnosis showed that patients treated with hypnosis experienced substantial benefits for many different medical conditions; it appears to be effective in alleviating chronic pain associated with irritable bowel syndrome (Gonsalkorale & Whorwell, 2005), cancer pain (Vickers & Cassileth, 2001), phantom limb pain (Oakley *et al.*, 2002), and migraine and tension headache (Olness *et al.*, 1987; Melis *et al.*, 1991; Sandor & Afra, 2005). An extensive recent review of clinical trials evaluating the effectiveness of hypnosis has been published (Stewart, 2005).

Hypnosis as a therapeutic approach of stress-related disorders may enhance treatment as a result of being a particularly persuasive form of communication. It may improve cognitive changes and enhance arousal management by decreasing exaggerated physiological responses to particular difficulties. Treatment employing hypnosis is now seen as involving not merely a reaction of traumatic memories, but working through them by assisting with the management of uncomfortable affect, enhancing the patient's control over them, and enabling them to cognitively restructure their meaning. The use of hypnosis can lead to changes in memory and the sense of self and view of others. Although this can be positive, it can also be negative. From the clinical perspective, we need to know the rationale for what we are doing so we can use hypnosis to recover memory. The clinician's familiarity with treating the presenting problem non-hypnotically is preeminent and critical to the application of hypnosis in identifying the most responsive conditions for treatment. The present chapter reviews much work on the central mechanisms of hypnosis, the engagement of cingulate cortex and its modulation for hypnosedation during surgical procedures. The documentation of objective outcomes and cingulate-mediated processing assures that biological mechanisms are being engaged.

Goals of This Chapter

Understanding the neuronal substrates of hypnosis has only been possible with the introduction of modern neuroimaging technologies. The advent of functional imaging provides a means of evaluating altered brain

function before, during, and after hypnotic interventions that are independent of subjective patient reports. Most importantly, for the present chapter, it is now possible to evaluate and model the specific mechanisms of forebrain processing based on objective changes in brain function. The application of hypnosis to surgical anesthesia provides an important cingulate-mediated mechanism of altering the flow of nociceptive signals throughout the pain neuromatrix and circuit models of these events leads to rationale methods of therapeutic intervention much like rational drug design based on ever more specific sites of drug action. In the present context, design refers to the method of hypnotic intervention and site specificity refers to subregions of cingulate cortex. The models presented in this chapter are the first step toward refining more specific targets and mechanisms of hypnotic actions in the cingulate gyrus. We seek to achieve the following specific goals:

1 Evaluate the hypnotic state and the role of cingulate cortex therein with a meta-analysis plotted onto a histologically analyzed brain to enhance identifying structure/function links.

2 Consider the role of aMCC in hypnoanalgesia.

3 Document circuit changes that subserve hypnoanalgesia with correlations in basal glucose metabolism in cingulate cortex.

4 Discuss the pharmacological mechanisms of hypnoanalgesia particularly in terms of opioids.

5 Present a formal circuit model of pre- and post-hypnotic mechanisms for pain control as a means of directing the rational development of more specific hypnotic interventions into cingulate cortex for pain syndromes and a myriad of other cingulate-mediated neuropsychiatric disorders.

Overview of the Hypnotic Experience

Hypnosis has gained respectability as a medical procedure, in large part, due to its demonstrated effects on pain and the validation of objective changes in brain function. It is less clear, however, whether hypnosis constitutes an altered state of consciousness. Hypnosis is characterized by highly focused attention as well as by heightened compliance with suggestions. This may lead to attentional and perceptual changes that would not have occurred had one been commonly vigilant. The hypnotic state also produces global changes in subjective experience reflecting a modulation of basic aspects of the body-self representation.

Table 17.1 summarizes some of the key features of the hypnotic experience that may be induced on the instruction of a therapist or self-induced by the subject. The extent that the phenomena are experienced and observed depends upon the depth of the hypnotic state, which is a characteristic of the subject and commonly referred to as hypnotic susceptibility or hypnotizability. Some of the most profound changes include altered awareness of sensory stimulation including nociceptive stimulation, distortions in reality or its temporal properties, alterations in voluntary muscle activity as well as in visceromotor systems including cardiovascular changes, visceral sensations and gland secretion. Finally, heightened imagery and expectations as well as a focus of personal attention inward or to narrowly defined events characterize the hypnotic state. Changes in sensory perception and the ability to internally alter the perception of reality provide an important means of interfering with information processing in the pain neuromatrix and to induce analgesia. To the extent that many of the events experienced during hypnosis can be associated with CNS changes using functional

TABLE 17.1 Hypnotic phenomena and relations to cingulate functions

Phenomena of hypnosis	Cingulate links
Reduction in awareness of sensory input	Feinstein *et al.* (2004)
Alteration in pain perceptions	Faymonville *et al.* (2000), Rainville *et al.* (2002)
Treatment and pain expectations	Petrovic *et al.* (2005), Kulkarni *et al.*(2005)
Error processing	Hester *et al.* (2005)
Expectation; attention shifting	Williams *et al.* (2000), Kondo *et al.* (2004), Egner *et al.* (2005), Weissman *et al.* (2005)
Alteration in voluntary muscle activity; relaxation, illusory movements, meditation	Sinha *et al.* (2004), Critchley *et al.* (2001)); Lou *et al.* (1999), Lazar *et al.* (2000), Naito *et al.* (1999)
Altered time perception	Corfield *et al.* (1995), Maquet *et al.* (1996a), Critchley *et al.* (2004), Hinton *et al.* (2004), Pastor *et al.* (2004), Pouthas *et al.* (2005)
Heightened imagery vividness or reality	Auditory imagery (Szechtman *et al.*, 1998; Yoo *et al.*, 2001); visual imagery (Gulyas, 2001)
Distortion of memory; true and false	Okado and Stark (2003)
Increased reality acceptance of fantasy experiences	Maquet *et al.* (1996b)

imaging and they are mediated by cingulate cortex, we need to link these experiences with hypnotically sensitive networks in the forebrain and that of the cingulate gyrus during hypnosis and hypnosedation.

Forebrain Mechanisms of Hypnosis

Positron emission tomography (PET) results indicate that hypnosis decreases activity in structures such as the right inferior parietal, precuneus, and posterior cingulate cortices, that are essential for the regulation of self-monitoring in healthy controls (Blakemore & Decety, 2001; Ruby & Decety, 2001; Perrin *et al.*, 2005). Pharmacological- (Fiset *et al.*, 1999) and pathological- (Laureys *et al.*, 2004) induced changes of consciousness also support this view. The coordinated activity within the thalamus, anterior cingulate cortex (ACC), the ventrolateral prefrontal cortex (VLPFC), posterior parietal cortex (PPC), and brain stem probably regulate the content of consciousness through mechanisms of executive attention (Mesulam, 1998).

The process of hypnotic induction, regardless of how it is implemented, serves to narrow a person's attention. It has been suggested that the effects of hypnosis are due to frontal inhibition (Gruzelier, 2000; Kallio *et al.*, 2001). The transient hypofrontality hypothesis suggests that the focused attention of the hypnotic state is the mechanism by which the activation of various prefrontal circuits is decreased, eliminating their contribution to immediate conscious experience. It appears that some cognitive function supported by the dorsolateral prefrontal cortex (DLPF), such as willed action, independent thinking, critical reflection and initiative, are affected in hypnosis. During hypnosis, suggestions become the predominant content in the working memory buffers without the higher cognitive computation provided by the DLPF circuits. Therefore, the person in hypnosis does not have the capacity to critically examine suggestions; they become executed by directly activating the motor system without being further scrutinized. Subjects' subjective description of their hypnotic experience states that their behavioral act appeared to happen by itself. This prefrontal hypofunctionality does not appear to be absolute, since subjects in the hypnotic state cannot be induced to act contrary to their moral belief or values (Kirsch & Lynn, 1998).

Functional neuroimaging studies have shown regional decreases in ventromedial prefrontal cortex (VMPFC) activity (Maquet *et al.*, 1999; Rainville *et al.*, 1999). This could reflect the clinical observation of decreased initiative for movement as observed in akinetic mutism (De Tiege *et al.*, 2003). The peculiar properties of hypnotic analgesia further point to the involvement of the prefrontal cortex in hypnosis. During hypnosis, one can ask a patient to intentionally ignore noxious stimuli. The sensation must first be recognized and then selectively blocked by modulating conscious awareness. This suggests a top–down process of the highest order and Crawford *et al.* (1993) proposed that increased blood flow in the orbitofrontal cortex might reflect attention system efforts to keep the emotional salience of the sensation from reaching consciousness. These observations are consistent with the hypofrontality hypothesis of hypnosis. Testing subjects using various neuropsychological measures, such as the Stroop task, showed impaired performance on tasks indexing frontally mediated supervisory functions during hypnosis, especially for high-hypnosis susceptible subjects (Dixon & Laurence, 1992). However, Stroop-test interference can be eliminated by hypnotic suggestions indicating that these suggestions must operate through a top–down mechanism that modifies the processing of input words through a means not voluntarily available (Raz *et al.*, 2002). A related result using neuroimaging indicated that the hypnotic instruction not to see color-prevented activation of prestriate areas related to processing color (Kosslyn *et al.*, 2000).

Studies measuring event-related potentials during hypnosis also indicate decreased prefrontal activation (Kaiser *et al.*, 1997; Nordby *et al.*, 1999). Croft *et al.* (2002) conducted a study in which electroencephalographic (EEG) spectral power was measured to painful electric stimuli. Gamma activity (32–100 Hz) over prefrontal scalp sites predicted subject pain ratings in the control condition. This relation was found unchanged by hypnosis in low-hypnotizable subjects, while it was lacking during hypnosis and hypnotic analgesia in high-hypnotizable subjects. This suggests that hypnosis interferes with the pain-gamma relationship in DLPFC. De Pascalis *et al.* (2004) in studies of gamma activity indicate that hypnotic suggestions in high-susceptible individuals modulate the activity of frontal and central areas of the cortex and these reductions were parallel to significant reductions in pain and distress ratings. Both observations support the view that hypnosis involves the suspension of a high-order attention system and other executive functions (Crawford & Gruzelier, 1992; Woody, 1994).

The dissociated control theory of hypnosis (Bowers, 1992) maintains that hypnotic inductions weaken frontal control of behavioral schemas, thereby allowing direct activation of behavior by the hypnotist's suggestions (Kirsch & Lynn, 1998). This theory received indirect support from rCBF studies, where increases in the right pregenual ACC area 32 were evoked during hypnosis using pleasant life experiences, while parts of medial and lateral prefrontal areas had a reduction in rCBF (Maquet *et al.*, 1999). In addition, hallucination of auditory stimuli in hypnosis activate area 32 in a manner

that is similar to the actual hearing of such stimuli, but not similarly to what happens in imagined hearing (Szechtman *et al*., 1998).

The available imaging and evoked potential observations generally agree that hypofrontal activity is a key part of the hypnotic state. In our consideration of the cingulate-mediated events during hypnosedation below, we do not explicitly model inactivation of DLPFC inputs into cingulate cortex or the changes in correlated activity because the neuronal mechanisms of these changes are not known. Finally, "hypofrontality" is only part of the cerebral change during hypnosis. Reductions in rCBF have also been observed in temporal lobes, posterior cingulate area 31, and the cerebellum (Maquet *et al*., 1999). Thus, the content of conscious awareness may be hypnotically regulated by reducing activity in a prefrontal, temporal, posterior cingulate, and cerebellar network. The following model will emphasize the activated flow of information in the cingulate gyrus during the hypnotic state, although reduced activity may be equally important.

Aspects of Hypnotic Experience Mediated by Cingulate Cortex

The hypnotic state is associated with an increase in rCBF in anterior cingulate area 32 and a reduction in posterior cingulate area 31 (Maquet *et al*., 1999). To the extent that cingulate cortex critically mediates the hypnotic state, it should be considered which aspects of this state can be attributed to it. The possible roles of cingulate cortex in hypnosis are summarized in Table 17.1. This table does not show responses of MCC to acute noxious stimulation as this is reviewed in detail in Chapter 14. In addition, although autonomic changes including heart rate, breathing, and blood pressure occur during hypnosis, these do not appear to be a direct response to cingulate activation but rather secondary, brainstem-mediated responses likely via the periaqueductal gray as discussed later. Autonomic changes mediated by cingulate cortex arise primarily via the projections of subgenual ACC to hypothalamic and midbrain autonomic nuclei and there is almost no evidence that sACC region has altered function in the hypnotic state.

Our hypnotic technique is based on reliving pleasant autobiographical experiences and pleasant imagery of past events. Area 32 in ACC is activated during happiness (George *et al*., 1995) and positive emotions (Phan *et al*., 2002; Vogt *et al*., 2003) and our hypnotic procedure increased activity in area 32 rostral to the genu in the external cingulate gyrus (Maquet *et al*., 1999). Mental relaxation and absorption in hypnosis correlates with ACC activity (Rainville *et al*., 2002). In addition, relaxing imagery (Sinha *et al*., 2004), biofeedback relaxation (Critchley *et al*., 2001), and meditation (Lou *et al*., 1999; Lazar *et al*., 2000) enhance activity in the ACC. In contrast, a recent study of Kulkarni *et al*. (2005) shows that attention to unpleasantness activates pregenual ACC in area 24 just caudal to the site associated with happiness and pleasant life experiences. This functional differentiation within ACC is pivotal to our model of the mechanism of hypnosis presented below.

A rich body of observations supports the role of cingulate cortex in most aspects of the hypnotic state as summarized in Table 17.1 (right column). This includes assessment of the duration of visual stimuli and altered memory, an altered sense of time, mental imagery, heightened expectations, and focused attention. A systemic literature review and plotting of activations in 18 major studies is provided in Figure 17.1. Studies during or after 1997 were included in which cingulate cortex was clearly demonstrated but not those in which the sites only slightly extended into cingulate cortex from adjacent areas with the primary activation focus. The cingulate map shows the distribution of rostral cingulate areas, regions and subregions as documented histologically in Chapter 3 and this case was co-registered to Talairach space. For each literature report, the relevant figure was digitally copied and co-registered to the case in Figure 17.1A using the corpus callosum, vertical plane at the anterior commissure (VCA), the cingulate and external cingulate gyri where present, and medial apex of the superior frontal gyrus. Let us consider the distribution of sites along three dimensions of the hypnotic state (Fig. 17.1B–D).

We begin by noting that our procedure employing pleasant life experiences activates a mid-dorsoventral level of area 32 (Fig. 17.1B, site #1). An important aspect of meditation altered consciousness involves an increase in activity in the pACC (Fig. 17.1B, #4); the exact same site that was also reported for the relaxation response by Rainville *et al*. (2002). When the latter investigators statistically removed relaxation-related variation from a response associated with absorption, a large and more dorsal site was generated in areas 32′ and 24′ of aMCC (Fig. 17.1B, #2). When activity associated with meditation was removed from that generated during resting normal consciousness, elevated rCBF was demonstrated in rostral area 32 (Fig. 17.1B, #3). Imagination of hearing a man's voice under hypnosis generated a large activation site mainly in area 32 in pACC (Fig. 17.1B, #5). Finally, conflict monitoring is one of the major functions of aMCC as discussed in Chapter 12 and in the study by Bush *et al*. (2000). Egner *et al*. (2005) generated high conflict in hypnotized subjects with a variant of the Stroop interference task and rCBF was increased within the cingulate sulcus in what appears to be the rostral and caudal cingulate motor areas (Fig. 17.1B, #6,

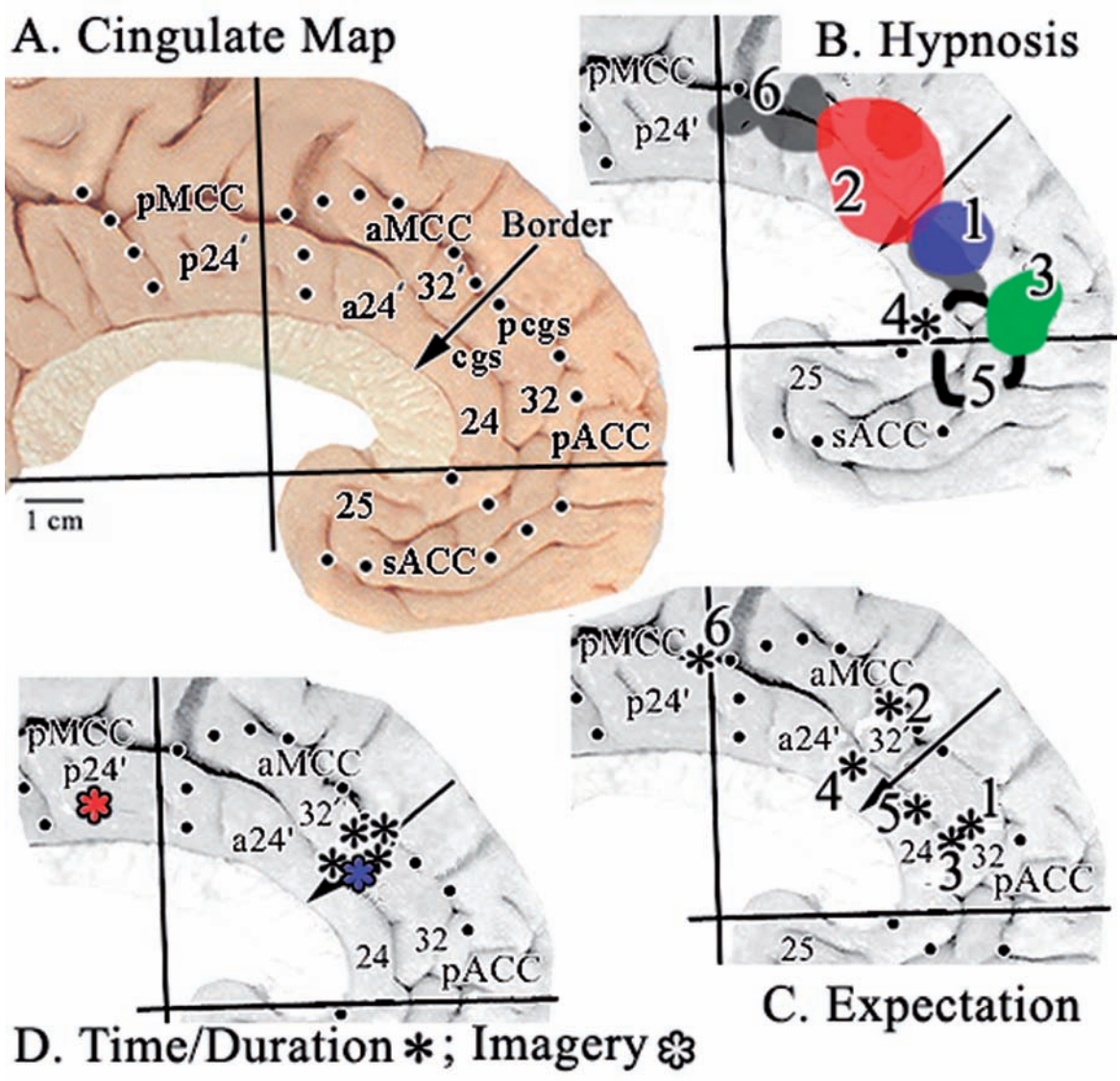

Fig. 17.1 Many cingulate-mediated cognitive functions are altered in the hypnotic state. Activations of pACC and MCC are plotted because these are either hypnotically sensitive (aMCC) or contain correlated clusters associated therewith (pACC). Figures B–D are copies of (A) with a reduced opacity and plots of activations associated with different cognitive paradigms. (A) Cingulate map of landmarks based on a histological case shown with an arrow to emphasize the "Border" between pACC and aMCC. cgs, cingulate sulcus; pcgs, paracingulate sulcus. (B) Six activations associated with the hypnotic/relation state: (1) Maquet *et al.* (1999), (2) Rainville *et al.* (2002), (3) Lou *et al.* (1999), (4) (*) Lazar *et al.* (2000), (5) Szechtman *et al.* (1998), (6) Egner *et al.* (2005). (C) Six sites associated with expectations were small enough that asterisks accurately reflect their locations; (1) Hester *et al* (2005), (2) Kondo *et al*, (2004), (3) Ernst *et al.* (2004), (4) Petrovich *et al.* (2005), (5) Kulkarni *et al.* (2005), (6) Weissman *et al.* (2005). (D) Black asterisks were not numbered because the sites were so closely aligned; Critchley *et al.* (2004), Maquet *et al.* (1996), Pastor *et al.* (2004), Pouthas *et al.* (2005); Blue asterisks, rostral, Yoo *et al.* (2001); Red asterisk caudal, Gulyas (2001).

shaded areas). Thus, the functions of aMCC and pACC are unique targets of hypnosis and this may include the cingulate motor areas. The procedure is not only specific within the cingulate gyrus, but by careful manipulation of the parameters used to induce and maintain the hypnotic state, one can target different parts of the anterior cingulate and external cingulate gyri.

A critical aspect of hypnosis is directing attention to particular processing modes and the control of expectations. Cingulate cortex is pivotal in this context along with prefrontal areas as discussed in "Forebrain Mechanisms of Hypnosis." Figure 17.1C shows plots of the findings of six studies in which conscious awareness, attention shifting and expectations were

manipulated and a cingulate activation was demonstrated; error processing with or without awareness (#1), attention shifting (#2), anticipation of a reward (#3), treatment expectation and placebo processing (#4), attending to the unpleasantness of a noxious thermal stimulus (#5), attending to task relevant cues (#6). It is interesting that the most dorsal site clearly extends into the cingulate sulcus and likely engages part of the rostral cingulate motor area and emphasizes the close linkage between stimulus cues and context and motor output. Thus, modulating and shifting attention and expectations alters activity in pACC and aMCC; the same regions engaged during hypnosis.

Estimation of time, stimulus durations, and mental imagery also alter cingulate functions, and Figure 17.1D shows that these activations in these studies are very close to each other at the border between ACC and MCC (arrow in Fig. 17.1A). The four studies shown for time assessment and stimulus duration involved detecting differences in the duration between light pulses (Maquet *et al.*, 1996; Pouthas *et al.*, 2005), the duration between two electrical pulses applied to the skin (Pastor *et al.*, 2004), and counting heart beats (Critchley *et al.*, 2004). Mental imagery of a monotone note generated activity that exactly overlapped temporal imaging (Yoo *et al.*, 2001; Fig. 17.1D, red rostral asterisk), suggesting that a temporal component may have been an important aspect of this task. Finally, imagery of letters in a national anthem activated area p24′.

It is surprising to see that time perception generates activity at the border between the ACC and MCC regions which is essentially in the middle of activated regions in subjects in the hypnotic state. It appears that alteration in the perception of time is fundamental to the hypnotic state and its location at this border assures that it is involved in most subjects almost regardless of the methodology employed.

Surgical Hypnoanalgesia

Hypnosis has been used for years to alleviate pain perception in laboratory settings and clinical pain conditions. It is effective for alleviating pain from cancer and other chronic pain problems like fibromyalgia, headache, diffuse low back pain, and that associated with irritable bowel syndrome as discussed earlier. Clinical studies also indicate that hypnosis can reduce acute pain experienced by patients undergoing burn wound debridement, children enduring bone marrow aspirations and women in labor (Patterson & Jensen, 2003; Stewart, 2005). More recently, hypnosis combined with light conscious intravenous sedation and local anesthesia has been proposed as a valuable alternative to traditional anesthetic techniques (Faymonville *et al.*, 1995, 1997).

Our clinical experience using hypnosis as an adjunct to conscious sedation and surgery performed under local anesthesia included more than 5000 patients. Indications for surgical procedures under local anesthesia and hypnosedation are listed in Table 17.2. Patients seen at our surgery department were given information concerning the possibility of performing the indicated surgery under hypnosedation by the surgeon. Deafness, severe psychiatric diseases, and allergies to local anesthetics were exclusionary criteria and informed consent was the first requirement for inclusion. The surgical decision to operate under local anesthesia and hypnosedation depends on the surgeon's own appreciation of feasibility and routine use of the technique. The method changes the working conditions because the patient is conscious during surgery. Finally, there is the necessity for very gentle manipulation and it requires a team effort and strong collaboration with the patient.

Most often patients were admitted fasting in the morning on the day of operation. They received a light premedication (Alprazolam 0.5 mg) and after transfer to operating theatre, heart rate, non-invasive blood pressure, SpO_2 and respiratory rate were recorded automatically. Each patient was invited to choose a very pleasant life experience to be relived during surgery. A hypnotic state was then induced using muscle relaxation and permissive and indirect suggestions. The induction procedure varied depending upon the anesthesiologist's observation of patient behavior and on her judgment of the patient's need. When the patient was thought to be at an adequate trance level

TABLE 17.2 Surgical procedures using routine hypnosedation

Minor	Major
Scar corrections	Thyroid lobectomy
Wisdom teeth	Total thyroidectomy
Protruding ears (children)	Cervicotomy for hyperparathyroidism
Septoplasty for nose fractures	Breast augmentation
Burn dressing changes	Head–neck lift
Face lift + blepharoplasty	Correction of mammary ptosis
Liposuction	Head–neck cancer with reconstruction
Breast adenomectomy	Septorhinoplasty
Turbinoplasty	Debridement–skin grafting
H Hysteroscopy	Calvarian bone graft (maxillofacial reconstruction)
	Tubal ligation
	Vaginal hysterectomy

at about 10 min after the beginning of the induction procedure with slow eye movements, the psychological approach was supplemented by administration of an anxiolytic and analgesic drug (very low doses) to maintain conscious sedation, provide patient comfort, and quiet surgical conditions. Local anesthesia provided by the surgeons was performed before incision. Throughout surgery, the anesthesiologist spoke to the patient. At the end of the operation, the anesthesiologist invites the patient to re-establish contact with the outside world. This serves to restore "normal consciousness" in a few seconds. The major benefit of this technique is to guarantee patient comfort during surgery and avoiding pharmacological unconsciousness. This anesthetic technique results in high patient satisfaction, better surgical convalescence, can be used in most motivated patients, and reduces the socioeconomic impact of hospitalization (Meurisse *et al.*, 1999; Defechereux *et al.*, 2000).

Hypnosis in the Pain Neuromatrix

Hypnosis-induced analgesia should be seen in the wider context of the pain neuromatrix. Pain is a complex, multidimensional experience comprising sensory-discriminative, motivational-affective and cognitive-evaluative components. According to the model of Melzack and Casey (1968), cognitive and affective processing is performed in parallel with sensory processing. Many of the ascending nociceptive pathways terminate in cortical and subcortical areas as discussed in Chapter 14 and functional imaging shows that areas activated during acute noxious stimulation include the periaqueductal gray (PAG), thalamus, striatum, primary and second somatosensory cortices (SI, SII, respectively), anterior insula, PPC, DLPF, ACC, and MCC (Derbyshire, 2000; Peyron, 2000). The basic nociceptive afferent pathway that is modulated during hypnosis is shown in Figure 17.2.

Although five parts of the cingulate cortex are involved in as many as five different roles in pain processing, it is the aMCC that appears pivotal to understanding hypnoanalgesia. Cognitive modulation of pain-related MCC activation has been shown not only by hypnosis but also by illusion (Craig *et al.*, 1996) and anticipation (Peyron *et al.*, 1999) and placebo (Petrovic *et al.*, 2002). The MCC is involved in assessing the motivational content of internal as well as external stimuli and in regulating context-dependent behaviors such as nocifensive behaviors (Devinsky *et al.*, 1995). From animal studies, we know that activation of the endogenous pain modulatory circuits requires specific extrinsic environmental cues or conditions. The environmentally induced analgesic response is prone to classical conditioning procedures during which the clinician or researcher suggests that a patient or volunteer experiences changes in sensation, perceptions, thoughts, or behavior.

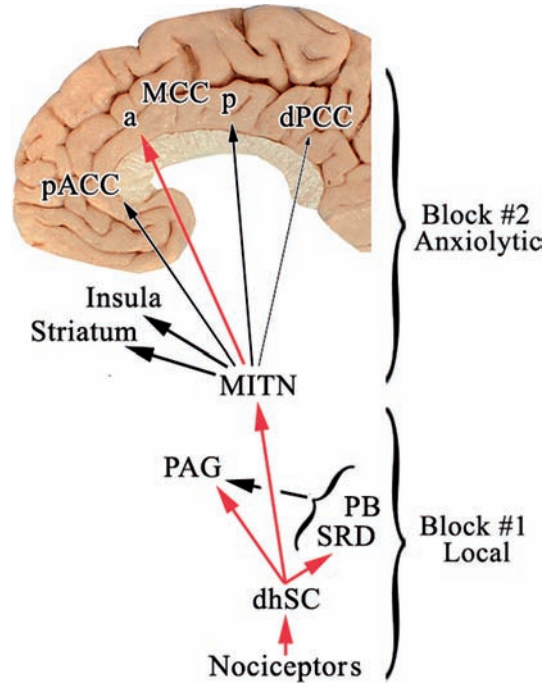

Fig. 17.2 Pain neuromatrix during initiation of the hypnotic state. The sources of nociceptive inputs to the medial pain system are shown transmitted through the midline, mediodorsal, and intralaminar thalamic nuclei (MITN) which drive cortical pain events. The size of the arrows suggests differences in the density of inputs with a major flow of nociceptive information to aMCC. During surgical preparation, patients receive a local anesthesia (Block #1) that greatly reduces transmission of nociceptors into the dorsal horn of the spinal cord (dhSC) and from there to the subnucleus reticularis dorsalis (SRD), and parabrachial nucleus (PB). Outputs to PAG and the MITN must be substantially decreased. A second block (Block #2) is induced with an intravenous anxiolytic agent to reduce the general flow of forebrain processing.

The hypnotic context is generally established by an induction procedure, using suggestions for relaxation, instruction to think about pleasant life experience to distract the patient or volunteers, without any reference to pain perception. We showed that this technique lowers both unpleasantness (i.e. affective component) and perceived intensity (i.e. sensory component) of acute noxious stimuli (Faymonville *et al.*, 2000). Hypnosis decreases both components of pain perception by approximately 50% compared to the resting state and by about 43% compared to a distraction task (mental imagery of autobiographical events). It has been shown that this modulatory effect of hypnosis is mediated by aMCC (Rainville *et al.*, 1997, 1999; Faymonville *et al.*, 2000).

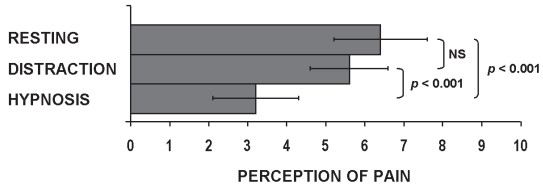

Fig. 17.3 Ratings of pain perception in the resting state, the distraction task (mental imagery of biographical memories) and in the hypnotic state. Values are means and standard deviations (NS, not significant). Adapted from (Faymonville *et al.*, 2003).

The effectiveness of pain relief during hypnosis and its central mechanisms are evaluated with psychophysicial measures of pain intensity and unpleasantness in resting, distraction, and hypnotic states. Figure 17.3 shows the mean visual analogue scale reports of pain during noxious heating of the right thenar eminence and shows that while distraction can reduce the pain signal, it is more profoundly impacted during hypnosis.

Mechanisms of Cingulate-Mediated Hypnoanalgesia

Studies examining brain activity during pain modulation by hypnosis showed modified activity in the midcingulate area a24a′. Using hypnotic suggestions, Rainville and colleagues (1997) induced powerful expectations of increased as well as decreased unpleasantness of experimental painful stimulation. This produced a specific modulation of a rostral part of aMCC activity and a modulation of pain unpleasantness.

Our study of the hypnotic modulation of pain processing and correlated changes in brain activity under hypnosis shows that "hypnoanalgesia" is produced by complex interactions among areas in the pain neuromatrix. Using PET and a factorial design with two factors: state (hypnotic state, resting state, mental imagery) and stimulation (warm non-noxious versus hot noxious stimuli applied to right thenar eminence), two cerebral blood flow scans were obtained with the O^{15} – water technique during each condition. Subjects were asked to rate pain sensation and unpleasantness. Statistical parametric mapping was used to determine the main effects of noxious stimulation and hypnotic state as well as state by stimulation interaction. Hypnosis based on reliving a pleasant life experience modulated both pain intensity and the unpleasantness of noxious stimuli in aMCC as shown in Figure 17.4 for pain intensity. The controls had no such correlation in aMCC. This shows that modulation of pain input during hypnosis alters blood flow in aMCC and that similar suggestions in control cases had no effect, i.e., there is no change in the slope of the line in control cases induced by hypnotic suggestions relating to pain intensity or unpleasantness. In addition, the interaction analysis showed that the activity in aMCC was related to pain intensity and unpleasantness differently in the hypnotic state than in the control situation with blood flow increasing in proportion to pain sensation and pain unpleasantness ratings.

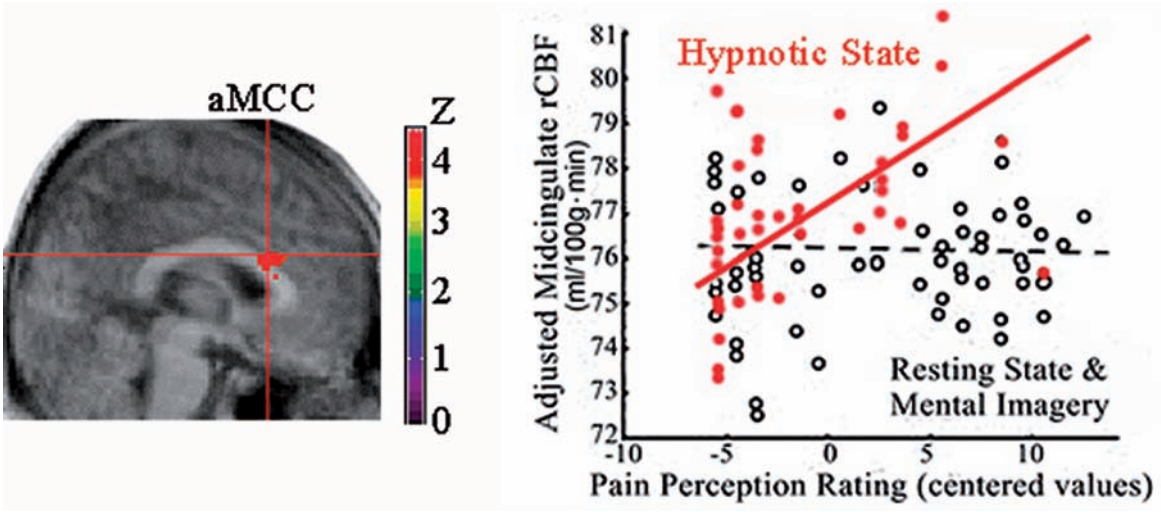

Fig. 17.4 (A) Activation in an area corresponding to area a24a′ correlates linearly with pain sensation ratings in the specific context of hypnosis (red on three-dimensional, spatially normalized MRI). (B) Plot of changes in pain perception ratings versus changes in adjusted blood flow in aMCC. Note the difference ($p < 0.05$) in regression slopes between hypnosis (red dots) and control conditions (circles). (Adapted from Faymonville *et al.*, 2000).

From clinical data, lesion studies, and single neuron activity (Foltz & White, 1962; Vaccarino & Melzack, 1989; Sikes & Vogt, 1992), we know that the activity of MCC codes the intensity of noxious stimulation. Functional imaging studies also conclusively show that MCC has an intensity code for noxious stimuli (Peyron *et al*., 1999; Tolle *et al*., 1999; Chapter 14). More recently, Büchel *et al*. (2002) showed that a region in the aMCC within the cingulate sulcus exhibits stimulus intensity-related– BOLD responses that are not related to pain intensity but to basic somatosensory processing. Stimulus-related activations were adjacent to the rostral cingulate premotor area, highlighting the strategic link of stimulus processing and response generation in this region. Ablation of the cingulum bundle underlying the aMCC in a case of obsessive-compulsive disorder, however, failed to alter the pre- and post-surgical perception of pain intensity (Greenspan *et al*., 2002; Chapter 18). Thus, while the ACC has been generally considered to be involved in the "suffering" component of pain (Kulkarni *et al*., 2005; Vogt, 2005) and affective reactions associated with pain unpleasantness, MCC activation is associated mainly with cognitive processes like response selection and motor regulation rather than pain perception *per se*.

The implication of the MCC in cognitive responses to pain has received support from recent pain studies, where attentional shifts to the noxious stimuli activate MCC, while sustained and voluntary directed attention to the stimulated region of skin activates area 32′. Preparation and/or inhibition of motor reactions are responses triggered by noxious stimulation and MCC is known to participate in motor planning (Devinsky *et al*., 1995; Picard & Strick, 1996), response selection (Turken & Swick, 1999), and motor learning (Jueptner *et al*., 1997). One important cognitive factor is the expectation regarding pain and the degree of certainty associated with an expectation. Behavioral studies have shown that subjective certainty that a particular aversive event is impending is associated with the emotional state of fear and leads to decreased pain sensitivity or hypoalgesia (Rhudy & Meagher, 2000). In contrast, uncertainty about the nature of the impending event is associated with anxiety and increased somatic and environmental attention and this may lead to increased pain sensitivity or hyperalgesia (Ploghaus *et al*., 2001). Functional imaging studies by Ploghaus and colleagues (2001) suggest that ACC is activated by fear which triggers descending opioid and non-opioid analgesic systems (Lichtman & Fanselow, 1991). Pain perception heavily depends on the expectation of the sensory consequences elicited by a noxious stimulus which relies on anticipation (Peyron *et al*., 1999) and pain may be associated with emotions produced by disequilibrium of the internal state of the body (introception; Sawamoto *et al*., 2000). Therefore, it appears that activity in aMCC is the target of our hypnoanalgesia procedure.

Cingulate Regulation of the Descending Noxious Inhibitory System

Access of ACC to the descending noxious inhibitory system (DNIS) may be pivotal to the mechanisms of hypnosedation. Our working hypothesis for cingulate-mediated mechanisms of hypnoanalgesia involves two basic concepts. First, the induction methodology selectively activates area 32 and its projections to the PAG to engage the DNIS. The pivotal role of the PAG in the DNIS was first described by Reynolds (1969) who used electrical stimulation of the PAG in rats to perform surgical procedures without the use of local or general anesthesia. Secondly, projections from the PAG inhibit the flow of nociceptive information out of the spinal cord and truncate nociceptive processing through the thalamus. The actions of the DNIS are well known and reviews of critical pathways are available (Depaulis & Bandler, 1991; Carrive & Morgan, 2004).

Cingulate inputs to the PAG

The PAG has a key role in descending mechanisms that modulate spinal nociceptive activity. In monkeys, descending projections are from layer V of multiple areas of the ACC including areas 25, 32, 24, and 24′, and a summary of the important findings of An *et al*. (1999; summary of schematic diagram in Fig. 15.10). The key findings are that highest projections to dlPAG arise from areas 32 and 25, moderate projections to both from a24b/c and lowest to vlPAG originate from a24b′. Obviously, the projection is greatest from the most rostral parts of the cingulate gyrus and they decrease in density at more caudal levels. This disproportionately large input from area 32 may be critical to the mechanisms of hypnosedation based on induction methods using pleasant life experiences.

Opiate intervention into the DNIS

Since the mid-1970s, it has been suggested that analgesia induced by hypnosis can be mediated by the release of endogenous opioids from the brain (Barber & Mayer, 1977; De Beer *et al*., 1985). Studies indicate that the administration of a pure opiate antagonist (naloxone) has no effect on analgesia induced by hypnosis (Barber & Mayer, 1977; Nasrallah *et al*., 1979; Knox *et al*., 1981; De Beer *et al*., 1985; Moret *et al*., 1991), while others have shown that naloxone could antagonize hypnoanalgesia (Stephenson, 1978). The study of Moret *et al*. (1991) further indicate that plasma β-endorphin levels remained remarkably unchanged during hypnosis-induced analgesia and concomitant naloxone administration and hypnotic pain relief.

The neurotransmitter systems involved in the antinociceptive effects of hypnosis were first explored by the use of pharmacological intervention. If similar endogenous opioid circuitry modulates pain transmission, it should be possible to define conditions under which hypnotic analgesia is produced and can be reversed with the selective opioid antagonist naloxone. Alternatively, the dose of naloxone may have been insufficient to affect pain. Naloxone can produce both hyperalgesia and analgesia, depending on the dose (Levine *et al*., 1979). Sometimes, it may act on pain-processing independent of placebo (Gracely *et al*., 1983), and in other cases, it may reverse placebo effects without producing hyperalgesia (Amanzio & Benedetti, 1999). Revealing the true pattern of naloxone–hypnosis interaction relies on interpreting both positive and null effects. Thus, to infer that there is no clinically meaningful effect of naloxone, statistical power and the use of within study positive controls are essential.

Hypnosis as well as drugs prescribed for various pain problems interact with internal self-regulatory mechanisms and context. There is compelling evidence that signals coming from the peripheral nervous sensory input undergo a complex modulation by cognitive, affective, and motivational processes when they enter the central nervous system. Previous imaging studies have shown that ACC is more reliably activated by opioids, whereas MCC is more reliably activated by pain. Reduced activation of the ACC is seen in conjunction with analgesic drugs like remifentanyl (Wise *et al*., 2002) or ketamine (Rogers *et al*., 2004) and also sedatives like propofol (Hofbauer *et al*., 2004). The ACC might play a key role in the cortical control of the brainstem during opioid analgesia (Krubitzer, 1990; Felleman, 1991; Vogt *et al*., 1995) by way of fiber tracts projecting directly to the PAG and the MITN.

It is unlikely that the ACC modulates pain perception/unpleasantness during hypnosis through pure attentional mechanisms. Attention processes refer generally to the information processing analysis of brain function and the response of the ACC to novel stimuli may reflect the intrinsic value of stimuli that have the potential to convey relevant information (Downar, 2002). The MCC region that was identified by Faymonville *et al*. (2000) has been related to pain processing, whereas the anterior portions of MCC are involved in attention demanding tasks (Derbyshire *et al*., 1998; Petrovic & Ingvar, 2002). A recent model of attention points further to the aMCC as a regulator of both affective and cognitive processes (Bush *et al*., 2000) and this was summarized earlier. Indeed, the activation of the aMCC during hypnotic pain modulation may reflect the role of this structure in the regulation of behavioral and emotional responses to pain and in the regulation of cognitive processes to cope with it.

Hypnotic Alteration of Cingulate/Forebrain Circuitry

To evaluate the mechanisms of the antinociceptive effects of hypnosis, Faymonville *et al*. (2003) assessed hypnosis induced changes in functional connectivity between aMCC and a large neural network involved in the different aspects of noxious processing. Complementary to the concept of functional segregation as a principle of organization of the human brain (i.e., localizing a function to a cerebral area), recent neuroimaging techniques have focused on functional integration (i.e., assessing the interactions between functionally segregated areas mediated by changes in functional connectivity). Functional connectivity is defined as the temporal correlation of a neurophysiological index, like rCBF, measured in remote brain areas. Monosynaptic anatomical connectivity, as demonstrated with neuroanatomical tracer studies in monkeys, is a necessary underpinning for the assessment of functional connectivity; however, such studies cannot be limited to anatomical findings because the human brain has areas that are not present in monkey (Chapter 3) and functional interactions cannot be demonstrated with strictly anatomical methods. A psychophysiological interaction means that the contribution of one area to another (i.e., regression slope) changes significantly with the experimental context (Friston *et al*., 1997).

The psychophysiological interaction analysis used in the present study aims at explaining the activity in one cortical area in terms of an interaction between the influence of a chosen area (i.e., MCC) and some experimental condition (i.e., being in a hypnotic state or not). Pain is a multi-dimensional experience including sensory-discriminative, affective-emotional, cognitive, and behavioral components and its cerebral correlate is best described in terms of neural circuits or networks, referred to as the "neuromatrix" for pain processing, and not as a localized "pain center" (Jones *et al*., 1991).

Using such studies of functional cerebral connectivity, it was shown that the hypnosis-induced reduction of pain processing mediated by the aMCC (Rainville *et al*., 1997, 1999; Faymonville *et al*., 2000) relates to an *increased* functional modulation between this MCC and a large neural network of cortical and subcortical structures known to be involved in different aspects of pain processing encompassing: prefrontal, pre-supplementary motor cortex (pre-SMA), insular, and pregenual cortices, striatum, thalami and brainstem as shown in Figures 17.5 and 17.6. These hypnosis-induced changes in connectivity between aMCC and prefrontal areas may indicate a modification in distributed associative processes of cognitive appraisal, attention, or memory of

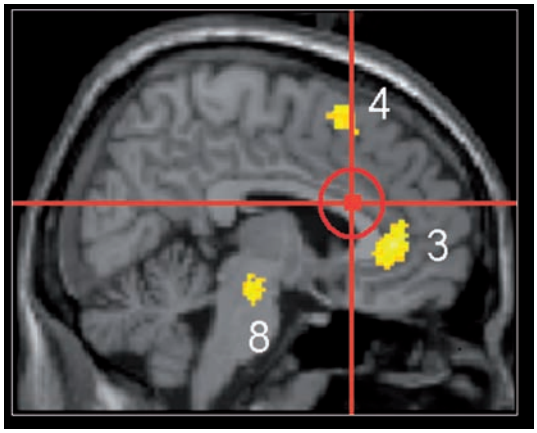

Fig. 17.5 The hypnosensitive region in area a24a′ (red) used to seed the correlation study is shown in the crosshairs. Notice that three areas have significant correlations on the medial surface (yellow): supplementary motor cortex (4), pACC (3), and PAG (8).

perceived noxious stimuli. As discussed earlier, frontal increases in rCBF have previously been demonstrated in the hypnotic state (Maquet *et al.*, 1999; Rainville *et al.*, 1999; Faymonville *et al.*, 2000). Frontal activation has also been reported in a series of studies on experimental pain (Kupers *et al.*, 2000; Kupers, 2001; Witting *et al.*, 2001; Bornhovd *et al.*, 2002; Lorenz & Garcia-Larrea, 2003), but the precise role of particular regions in the central processing of pain remains to be elucidated (Treede *et al.*, 1999). The MCC has also a major role in skeletomotor function (Fink *et al.*, 1997). Its increased functional relationships with pre-SMA and striatum during hypnosis may allow the MCC to organize the most appropriate behavioral response, taking into account the pain perception and possible outcomes. Indeed, the basal ganglia encode and initiate basic movement patterns expressed through premotor and primary motor areas and show frequent activation to noxious stimuli (Jones *et al.*, 1991; Coghill *et al.*, 1994; Derbyshire *et al.*, 1997; Derbyshire & Jones, 1998). The basal ganglia are not exclusively linked to motor function but have also been proposed to support a basic attentional mechanism facilitating the calling up of motor programs and thoughts (Brown & Marsden, 1998) and are part of closed-loop mechanism as described in Chapter 28.

The anterior insular cortex and the ACC are known to show the most consistent activation in functional imaging studies on pain perception (Ostrowsky *et al.*, 2002; Peyron *et al.*, 2002). The insula is thought to take an intermediate position between the lateral (sensory-discriminative) and medial (affective-emotional) pain systems. It receives major input from the somatosensory system (Mesulam & Mufson, 1982), has direct thalamocortical nociceptive input and, through its projections to the amygdala, has been implicated in affective and emotional processes (Augustine, 1996). The observation of an increased MCC-insular modulation during hypnosis is in line with its proposed role in pain affect

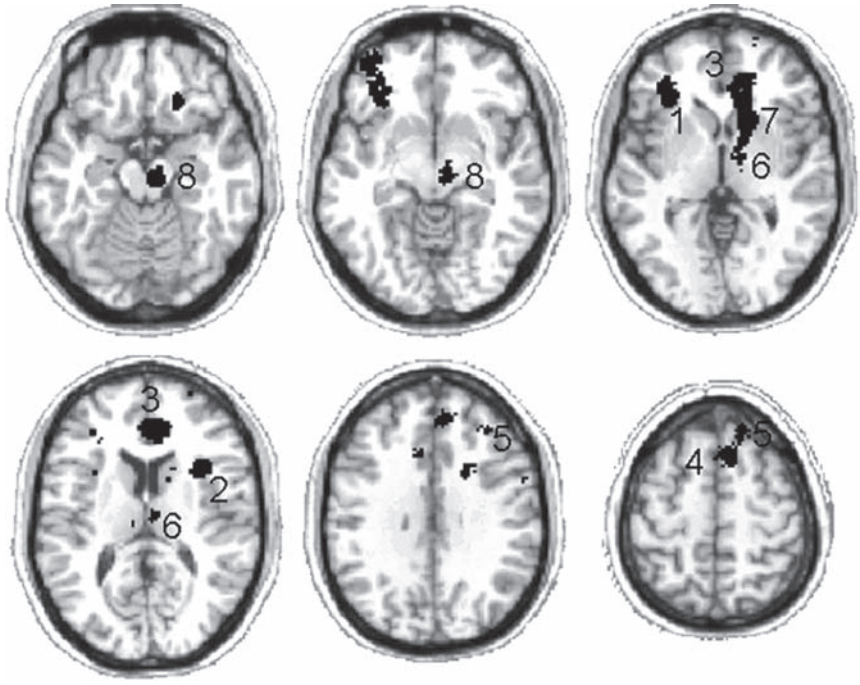

Fig. 17.6 Regions with hypnosis-related increased functional connectivity with aMCC (Fig. 17.5 in red crosshairs) and significant correlations with (1, 2). Left, right insula (3) pACC; 4.pre-SMA (5) Superior frontal gyrus (6) Right thalamus (7) Right caudate nuc. (8) Midbrain-PAG (Faymonville *et al.*, 2003).

(Rainville *et al.*, 1999) and pain intensity coding (Craig *et al.*, 1996). In the light of the "somatic marker" hypothesis of consciousness (Damasio, 1994), the right insular cortex has been hypothesized to be involved in the mental generation of an image of one's physical state underlying the attribution of emotional attributes to external and internal stimuli.

The observed increases in functional connectivity between the MCC and the thalamus and midbrain during hypnosis could be related to pain-relevant arousal or attention (Kinomura *et al.*, 1996). The thalamus has been shown to correlate with pain threshold, whereas activation of the midbrain is correlated with pain intensity (Tolle *et al.*, 1999). It is tempting to hypothesize a hypnosis-related subcortical gating on cortical activation that underlies the observed decreased subjective pain perception. Previous studies have shown that different forms of defensive or emotional reactions, analgesia and autonomic regulation are represented in different regions of the PAG (Bandler & Shipley, 1994).

The pACC and insular cortices and thalami are also known to be implicated in autonomic regulation (Bandler & Shipley, 1994; Augustine, 1996). The observed modulatory role of the MCC on this network could explain the clinical finding that patients undergoing surgery during the hypnotic state show modified autonomic responses and less-defensive reactions in response to an aversive encounter (Faymonville *et al.*, 1997).

Circuit Model of Hypnoanalgesia

Some rules of circuit modeling

Monosynaptic cortical connections in the monkey forebrain are usually summarized in terms of diagrams that suggest flows of information within complex circuits. These diagrams attempt to summarize the main findings and provide interpretive insights into particular functional mechanisms. With the introduction of functional correlative methods for analyzing "circuits" with human imaging modalities, circuit diagrams are needed to characterize the flow of information and hypnotically induced changes in the valence and intensity of particular connections. Since the interpretation of changes in circuitry is complex and given to many alternatives, a formal set of rules are required to guide the modeling process and some of our guiding principles are briefly considered here.

Monkey monosynaptic connections are used when a comparative area is known to exist in human brain. Area 32′, caudal area 31, cortex on the dorsal bank of the cingulate sulcus, area 33, and area 26 do not exist in the monkey brain, according to the comparative anatomy discussed in Chapter 3, and cannot be assessed in monkey. All other areas in the human cingulate gyrus, however, have counterparts in the monkey and can be analyzed with experimental tract tracing methods. Of course, simply because two areas are shared by two species, this does not mean they have the same connectivity; however, this assumption is made until further evidence is available.

A simple connection between two areas does not mean they will be included in a model of hypnoanalgesia because there are many connections that may be dormant during hypnosis or, as in the term hypofrontalitiy, may be inactivated and drop out of a functional circuit. Only those connections demonstrated in some meaningful way to be involved in a particular process can be included and this is why the correlation studies during hypnosis and hypnoanalgesia are of particular importance.

Although a high correlation of functional activity between two areas suggests they are simultaneously positioned to share information, this does not mean they are "connected." For example, although there are reciprocal connections between the sulcal and dorsal bank of the cingulate gyrus with the insula, insular "connections" with area a24a′ on the ventral cingulate gyral surface shown in the correlation study do not exist in the monkey (Chapter 6) and cannot be viewed as part of the hypnotic modulation of pain circuitry. Since the insula and aMCC receive a parallel input from the MITN (Vogt & Sikes, 2000), the source of the correlation may be via co-modulation of both areas at a low level of activity by the MITN.

Correlated functional activity between two areas does not mean that they share an elevation in activity. A correlation could become more striking as two areas have jointly reduced activity; possibly reaching baseline values. Thus, correlation does not equate to excitation. In contrast, there are heavy and reciprocal connections between DLPFC and almost the entire cingulate gyrus (Chapter 5). This wide projection could be either an inhibitory, baseline (not discharging), or excitatory during hypnosis, and this is correlated with activity in MCC that may be associated with excitation in the DNIS.

Finally, a correlated change cannot be shown with an arrow between two areas if there is a single source of input to both that equally explains the change. In other words, the simplest pathway between two structures must be used as in the MITN connection for the anterior insula and aMCC when it is clear that this is the most likely source of correlated changes. Also, corticocortical connections are much less dense than thalamic afferents and the latter usually serve to define the primary functions of a region. The only instance in which this is not the case is during "top–down" functions of particular cingulate regions,

where the cortex itself is generating the primary activity rather than the sensory or motor inflow from the thalamus.

Hypnotic block of thalamocingulate processing: Key to hypnoanalgesia

The model in Figure 17.7 shows the structures with activity correlated with that of area a24a′ during hypnosis. The functional hypnotic circuit was derived from this information along with imaging in different states and paradigms, monkey connection studies and neurophysiological assessment of the functions of particular components of the circuit. The initiation of activity begins with hypnotic driving of pACC by imagery of pleasant events that drives much of the PAG and DNIS along with the aMCC. Key to understanding this circuit is the three blocks numbered on the right of the diagram that indicates termination of nociceptive transmission through the MITN.

The specific connections and organizational patterns are shown in the functional circuit for the following reasons: (1) Since area 24 may be involved in the unpleasantness of nociceptive stimuli (Ploner *et al.*, 2002; Kulkarni *et al.*, 2005), we must assume that the active region during hypnosis in the circuit model is focused on area 32. (2) Since area 32 projects to area a24a′/b′ (Arikuni *et al.*, 1994) and these two areas have correlated activity, an active projection is shown in the other direction between these areas. (3) Both cingulate areas project substantially to the striatum and may be involved in open-loop reward systems (Chapter 28) that could be active during hypnosis. (4) The hypofunctional DLPFC is shown with white arrows as it may not contribute to processing in the circuit. (5) Both cingulate areas and the dysgranular insula project to the PAG as discussed previously and these projections to the PAG are pivotal to inducing a diffuse analgesia via the DNIS. Activation of the insula could be generated in a

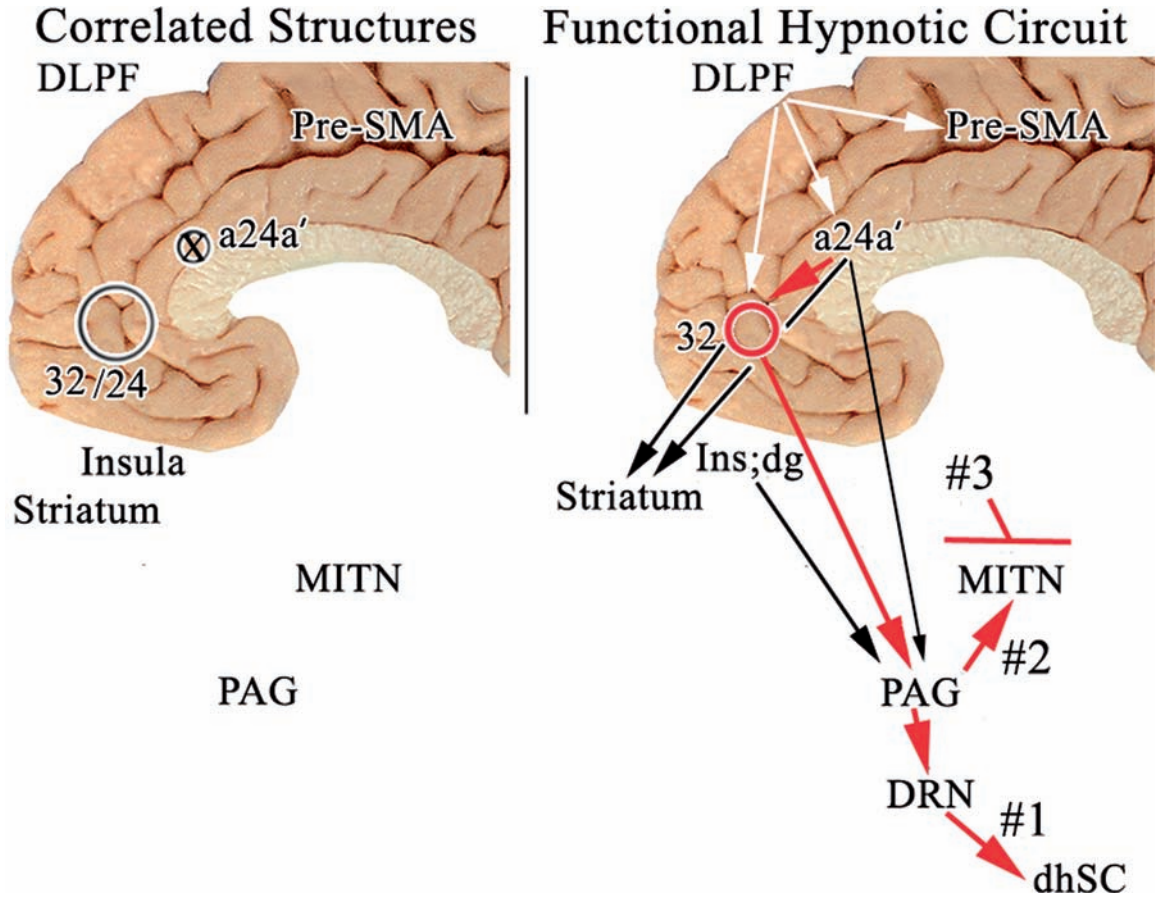

Fig. 17.7 Left: Summary of regions with correlated activity to a24a′ at "x" and a functional circuit derived from this and other information (Right). Since the exact nature of DLPFC engagement with cingulate cortex is not understood, this connection is noted with a triad of white arrows. The largest black arrows indicate the predominant pathways associated with hypnotic activation of the DNIS that leads to block of output from the dorsal horn of the spinal cored (dhSC, #1), PAG block of MITN output (#2) and truncation of nociceptive processing through the MITN (#3). Ins; dg, dysgranular insula; DRN, dorsal raphe nucleus.

manner similar to that of area 32, since a general sense of the body state may be activated with pleasant living experiences. The projection of area a24a′ is less dense than the other two and is shown with a thin arrow. (6) Electrical stimulation of the PAG inhibits nociceptive activity in the MITN including the centrolateral, parafascicular and mediodorsal nuclei (Andersen, 1986) and this provides for one of two mechanisms for blocking nociceptive transmission through the MITN to the pain neuromatrix including MCC. (7) Nociceptive, wide-dynamic range, spinothalamic tract projection neurons are inhibited via projections that originate in the PAG (Zhang *et al.*, 1991) possibly via a synaptic connection in the nucleus raphe magnus (Giesler *et al.*, 1981). These projections generate the primary block of nociceptive processing through the MITN shown in Figure 17.7. (8) Both blocks of nociceptive processing through the MITN (one mediated by the thalamus and one by inhibition of nociceptive projections out of the spinal cord) result in a functional inhibition at #3 in Figure 17.7. This is the pivotal mechanism by which nociceptive transmission during hypnosis is blocked during surgical intervention.

Hypnosis as an Interventional Alternative

Hypnosis can be viewed as a particular cerebral waking state where the subject, seemingly somnolent, experiences a vivid, multimodal, coherent, memory-based mental imagery that invades and fills the subject's consciousness. The pattern of cerebral activation, measured by means of PET, during the hypnotic state differs from that induced by simple mental imagery. The reduced pain perception during hypnosis is mediated by an increased functional connectivity between the MCC, the insula, and pACC and the PAG. The pleasant life experiences employed to induce and maintain hypnosis likely activate areas 32, the dysgranular insula, and the striatum. The functional block of processing through the pain neuromatrix appears to be blocked in the MITN via projections into the PAG. These findings point to a critical role for the ACC and MCC in hypnosis-related alteration of sensory, affective, cognitive, and behavioral aspects of nociception. This view reinforces the idea that not only pharmacological but also psychological strategies for relieving pain can modulate the interconnected network of cortical and subcortical regions that participate in the processing of painful stimuli.

Hypnosis produces objective changes in brain function and these can be demonstrated with functional imaging. The pivotal role of MCC in hypnosis and its role in executive functions and extensive connections with motor systems provide a target for therapeutic interventions. Indeed, hypnoanalgesia targets this region and future modifications in the method may lead to even more effective means of truncating the flow of nociceptive information through the MITN.

The future for hypnosis in controlling medical illness seems almost limitless and enhanced targeting of subregions of the cingulate gyrus to regulate pain during surgery is only the first step. There is a large number of psychiatric conditions that may be usefully addressed by targeting cingulate subregions for therapeutic intervention for acute and chronic stages of disease expression and many of these are discussed in the present volume. Diffuse functional disorders such as irritable bowel syndrome, fibromyalgia, trigeminal neuralgia and diffuse low back pain have no apparent organic basis in peripheral organ structure or chemistry and appear to primarily result from dysfunction of CNS structures including prominent impairment of cingulate functions. Post-traumatic stress and obsessive-compulsive disorders are complex syndromes that may be treated with hypnotic intervention into the cingulate gyrus.

At this point, it seems reasonable to invoke the model of rational drug development when considering the outlook for hypnotic intervention into pain and psychiatric disease states. In drug development, a molecule is synthesized with ever greater specificity for a particular receptor subtype. In terms of hypnosis, hypnotic methodology is altered in such a way to generate activity in particular parts of the cingulate gyrus. Thus, the treatment of acute and chronic diseases that are mediated by cingulate cortex requires continually refining the method to enhance its specificity for particular outcomes in conjunction with objective measures of cingulate mechanisms with high-resolution imaging techniques.

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