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Review

Localization of function in anterior cingulate cortex: From psychosurgery to functional neuroimaging

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ABSTRACT

Early localizationists linked anterior cingulate cortex (ACC: Brodmann's area 24 and adjacent regions) with emotional behavior, paving the way for bilateral cingulotomy psychosurgery in severe, treatment resistant, cases of obsessive–compulsive disorder, chronic pain, depression, and substance abuse. Neuropsychological follow-up of such cases demonstrated executive function impairment. Abnormal neuroimaged activity in ACC has been found in many psychiatric conditions, including obsessive–compulsive disorder, chronic pain, substance abuse, and schizophrenia. With healthy participants, increased neuroimaged activity in ACC has been linked with challenging executive function tasks, homeostatically incongruous physical states, and the encoding of the pleasant/averseness of stimuli. There is disagreement on the cortical substrate subsumed by the term ACC, the existence of functionally distinct ACC subregions (e.g., dorsal: cognitive vs. ventral: emotion), and the interpretation of functional neuroimaging studies. Synthesis of neuropsychological and functional neuroimaging studies suggests ACC contributes to behavior by modifying responses especially in reaction to challenging cognitive and physical states that require additional effortful cognitive control. This is accomplished by monitoring the emotional salience of stimuli, exerting control over the autonomic nervous system, and modulating cognitive activity.

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1. Introduction

Broca (1861) is credited with being the first to localize a complex cognitive function to a specific region of the human cortex, thereby founding the science now known as clinical neuropsychology (Ryalls and Lecours, 1996). Over 150 years later, localization of function in the human cortex, while precisely defined for certain regions like primary sensory and motor cortices, remains uncertain for many parts of association cortex, including that lying within the frontal lobe. Frontal association cortex has three major neuroanatomical subdivisions: dorsolateral, orbitofrontal, and ventromedial (Alvarez and Emory, 2006). These all mediate *executive functioning*, a broadly defined subcomponent of cognitive behavior that has defied consensus dissection into its constituent processes (Lenartowicz et al., 2010; Packwood et al., 2011; Stirling and Elliott, 2008), a necessary prerequisite for localization (Luria, 1973).

Anterior cingulate cortex (ACC) is an anatomically distinct subregion of ventromedial frontal cortex consisting of the cingulate sulcus and gyrus that lie dorsal to the corpus collosum and ventral to the superior frontal gyrus. It encompasses Broadmann's area 24 and adjacent regions. It is often subdivided into anterior (variously termed rostral, ventral, and genual) and posterior (caudal, rostral, or midcingulate) subregions. It has extensive bidirectional

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connections with dorsolateral, orbitofrontal, primary and secondary motor, and insular regions of the cerebral cortex.

There has long been speculation concerning the behavioral function of ACC. Early localizationists linked ACC with the rhinencephalon and olfactory functions until Papez (1937) used data from neuroanatomical dissection and animal lesion studies to conclude: "the hypothalamus, the anterior thalamic nuclei, the gyrus cinguli, the hippocampus and their interconnections constitute a harmonious mechanism which may elaborate the functions of central emotion" (p. 743). This circuit now forms part of what is widely known as the *limbic system* whose behavioral function was elaborated by MacLean (1952) as: "a visceral brain that interprets and gives expression to its incoming information in terms of *feeling*" (p. 415: italics as in original). *Limbic* (from *limbus* meaning border in Latin), was originally used by Broca (1878) to describe a "lobe" on the medial and basilar surfaces of the cerebral hemispheres that formed the border around the brainstem. It is now seen as unlikely that the limbic system operates as a single unit (e.g., Devinsky et al., 1995).

As noted by Papez (1937), occlusion of any of the eight branches of the anterior cerebral artery or other naturally occurring neurological condition rarely affects ACC in isolation, restricting human lesion/behavioral change correlational analysis. An alternative source of such data comes from the practice of cingulotomy psychosurgery that has been used on a very limited basis with severely disturbed, treatment resistant, psychiatric cases for over 60 years. In advancing an understanding of brain/behavioral relationships, such cases have an advantage over naturally occurring brain injuries in that the lesions (about 1 cm in diameter and 2 cm in vertical length bilaterally: Ballantine et al., 1987) are precisely limited to ACC.

This review combines information learned from studies involving neuropsychological lesion analysis of cingulotomy patients with that from functional neuroimaging studies of psychiatric and healthy participants that have focused on ACC. The goal is to arrive at a parsimonious understanding of the contribution of ACC to behavior.

2. Emotional changes and cognitive impairment following bilateral cingulotomy psychosurgery

Pioneering research in monkeys found that stimulation of ACC produced autonomic nervous system responses and bilateral ACC lesions resulted in "increased tameness and reduction of aggressiveness, with apparent loss of the sense of danger" (Glees et al., 1950, p. 189). These findings paved the way for bilateral cingulotomy psychosurgery for which it was initially reasoned: "one would expect greatest improvement not in schizophrenics, but in those anankastic cases whose obsessions or compulsions are charged with fear somehow referable to their fellows" (Ward, 1948, p. 443). It (and variants like cingulectomy) has subsequently been used to treat a variety of diagnostic conditions, primarily: obsessive–compulsive disorder (Dougherty et al., 2002; Jenike et al., 1991); emotional concomitants of chronic pain (Foltz and White, 1962); depression (Ballantine et al., 1987); and substance abuse (Balasubramaniam et al., 1973). Modern proponents report it is experiencing a renaissance in some countries with the development of increasingly sophisticated surgical techniques, while admitting that safety and efficacy have not been adequately established (Brotis et al., 2009; Matthews and Eljamel, 2003).

Bilateral cingulotomy results in less severe disruption to patient personality than prefrontal leucotomy (Whitty et al., 1952) and post-operative changes have been described as a "slight, but consistent. . .reduction of inhibition, perseveration, and excessive self-concern" (Tow and Whitty, 1953, p. 193). Success rates range from 30 to 80% (Balasubramaniam et al., 1973; Brotis et al., 2009) with much of the variability due to differing definitions of "success".

Historically, follow-up of bilateral cingulotomy cases suggested no secondary cognitive impairment (e.g., Ballantine et al., 1987; Faillace et al., 1971). Neuropsychological symptoms traditionally linked with bilateral ACC lesions like akinetic mutism (immobility and lack of communication without muscle paralysis), were discovered to invariably involve damage to additional brain structures (Devinsky et al., 1995; Nemeth et al., 1988). More recent reports have contradicted the earlier findings in showing that bilateral cingulotomy psychosurgery is associated with impairment of executive functions. All such studies have either very low *N* or are single case studies.

Cohen et al. (1999) administered a comprehensive battery of neuropsychological tests within a pre-post longitudinal design to 12 cingulotomy chronic pain cases with matched controls. In the immediate postsurgical state, mutism, akinesis, blunted affect, lethargy, and apathy were common but these symptoms resolved rapidly. At one year postsurgery, most neuropsychological test scores were normal but persisting deficits were found in spontaneous utterances and on two neuropsychological tests of spontaneous response production (Design Fluency and Object Construction). Performance on the Stroop Color and Word Test was impaired at 3 months follow-up in the color naming but not the interference condition. Janer and Pardo (1991) reported similar Stroop findings at 2 weeks follow-up for a single case that, at 8 months follow-up, had no neuropsychological deficits. Ochsner et al. (2001) also described a single case study where the patient (who had been diagnosed with obsessive–compulsive disorder, major depression, and anorexia nervosa) exhibited multiple executive function deficits postsurgery, but the results are difficult to interpret as the patient had a history of traumatic brain injury with seizure disorder and the evaluation took place three days after surgery when generalized cognitive impairment that resolves rapidly is expected. Ridout et al. (2007) found nine cingulotomy depressive patients tested 12–46 months postsurgery were impaired on a test of emotional recognition compared to both depressed and normal controls. For all these groupings combined, Stroop error scores were found to predict emotion recognition accuracy. Other tests of executive function, (e.g., Verbal Fluency), showed no significant impairment. Yen et al. (2009) reported the Stroop interference condition was the only measure impaired at 1 week postsurgery in a group of 10 cingulotomy patients who underwent treatment for intractable cancer pain. This impairment had resolved by 1 month.

All neuropsychological studies of bilateral cingulotomy psychosurgery patients implicate the Stroop Color and Word Test. Introduced over 75 years ago (Stroop, 1935), this test has many design variations but the essential component involves two timed comparison conditions: (a) color naming (i.e., color words printed in matching colors, e.g., *GREEN* printed in green ink), with the task being to read the color word; and (b) interference (color words printed in nonmatching colors, e.g., *GREEN* printed in red ink) with the task being to report the color of the ink. The interference condition is associated with the *Stroop effect*, usually measured as a significant slowing of performance (sometimes by increased errors), that is thought to result from inhibition of the automatic tendency to read the word. This skill is generally considered to be a subcomponent of executive function often referred to as *response inhibition* that occurs during response selection and not stimulus encoding (Donohue et al., 2012).

Neuropsychological studies that have linked impaired Stroop performance with naturally occurring brain lesions have reported highly inconsistent results. Exaggerated Stroop interference effects have been associated with: left frontal lesions (Perret, 1974); left ACC lesions (Swick and Jovanovic, 2002); right lateral frontal lesions