Impairment of executive functions in a patient with a focal lesion in the anterior cingulate cortex. Evidence from neuropsychological assessment

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Summary

Patients with naturally occurring lesions involving the anterior cingulate cortex are rare and there thus exist very few reports of focal lesions in this area. We report a longitudinal study of a new case of selective anterior cingulate damage due to the presence of an angiocavernoma at the junction of the anterior third with the middle third of the right gyrus cinguli. Before surgery, the results of several, different tests suggested a significant impairment of executive functions, including deficits in planning, monitoring of ongoing behavior, and strategy shifting, as well as an exaggerated susceptibility to retroactive interference. Most of these symptoms disappeared completely or almost completely after the surgical removal of the angiocavernoma, although exaggerated susceptibility to interference was found to persist four months after surgery.

KEY WORDS: anterior cingulate cortex, executive functions, retroactive interference.

Introduction

The cingulate cortex has been classically regarded as part of the Papez circuit, and thus involved in emotion. In recent decades, experimental studies have provided convincing evidence that, within the cingulate cortex itself, along the rostral-caudal axis, there exist two distinct regions subserving different sensory, motor, and cognitive functions: the anterior cingulate cortex (ACC) and the posterior cingulate cortex (1). The ACC can, in turn, be further subdivided into a rostral, affective component, which includes Broadman's areas 25, 33, and the rostral part of area 24, and a caudal, cognitive component, which includes the remaining part of area 24, and area 32 (2).

Anatomical studies in non human primates have demonstrated the existence of strong, reciprocal connections between the caudal part of the ACC and the dorsolateral prefrontal, and inferior parietal cortices (3). This distributed neural network is thought to mediate higher order control processes termed executive functions.

The remarkable development of non invasive, functional, brain imaging techniques has made it possible to demonstrate, directly in humans, the involvement of the different brain areas in different cognitive processes. Studies employing positron emission tomography, as well as functional magnetic resonance imaging, showed significantly increased ACC activation when subjects were engaged in a wide range of tasks believed to depend upon executive functions, such as the Stroop Interference task (4), the Tower of London task (5), the Verbal Fluency Test (6), and several working memory tasks, irrespective of the sensory modality of the stimulus (7), or the nature of the material used: verbal (8), numerical (9), or pictorial (10). However, the exact nature of ACC involvement in executive processes, is still a matter of debate. Barch et al. (11) suggested that the ACC is generically involved in the mediation of motivational aspects of behavior, whereas D'Esposito et al. (8) argued that it serves to allocate attentional resources among competing stimuli during the performance of concurrent tasks. More recently, several fMRI studies have provided evidence in favor of the so-called conflict detector hypothesis, according to which the ACC is activated whenever interference or interactions between incompatible information processing pathways give rise to response conflict (6,12,13).

Finally, clinical evidence, too, seems to support the argument that the ACC plays a crucial role in executive functions. Psychiatric patients who have undergone bilateral anterior cingulotomy for the relief of drug-refractory behavioral disorders provide the main source of information on ACC damage. Whitty and Lewin (14), who first addressed this problem, reported that, after the disappearance of a transient confusional state, patients showed a slight memory disorder characterized by a defective temporal localization of events. Subsequent studies on psychiatric patients submitted to surgery, reported impaired allocation of attentional resources as the main effect of cingulotomy (15,16). Naturally occurring pathologies involving the ACC in isolation are rather rare. Laplane et al. (17), describing a patient with a hemorrhagic, bilateral lesion of the ACC, reported exaggerated distractibility, and difficulty sustaining the attention needed to perform a goal-directed activity. More recently, two other patients submitted to partial resection of the right ACC because of tumor, have been described. Turken and Swick (18)

presented their patient with three different tasks requiring either manual or vocal responses. The patient performed within the normal range when asked to give vocal responses, but very poorly when required to give manual responses, thus demonstrating an intact ability to produce correct decisions, but a specific impairment in selecting the appropriate output modality. Danckert et al. (19) presented their patient with two different flanker tasks, a paradigm widely used to study interference effect. When flankers were presented in the visual field contralateral to the ACC lesion, the patient showed an abnormal susceptibility to interference, which was interpreted as the consequence of a difficulty in monitoring response conflict between stimuli competing for the allocation of attentional resources.

Here, we describe a new case of selective ACC damage. Although rather descriptive, this case nevertheless provides further support for the hypothesis of ACC involvement in executive functions.

Case report

MPT, born in 1934, is a right-handed, retired manual worker, with 5 years of schooling, and no history of major illnesses. On January 19th 1999, at around 10.30 a.m., just after returning home from shopping, MPT suddenly felt confused and spatially and temporally disoriented. In particular, she was absolutely unable to recall what had occurred earlier that morning. About three hours after the onset of the confusional state, MPT was admitted to hospital. It is noteworthy that during this time no loss of consciousness was observed, and the patient was always alert and cooperative. On admission, both somatic and neurological examinations were negative as was CT scan. However, MPT seemed confused and showed temporal but no longer spatial disorientation. Her recollection of recent events was vague, but without confabulation. Within a few hours, normal memory faculties were recovered. The following morning MPT showed no residual memory disturbance apart from lacunar amnesia. Thus, a diagnosis of transient global amnesia was made, and the patient was discharged from hospital. Since then, MPT has never experienced any similar episodes. However, an MRI investigation, performed one week after discharge, showed a small area of altered signal intensity at the junction of the anterior third with the middle third of the gyrus cinguli on the right hemisphere (Fig. 1a). A few days later, a digital angiography of the epiaortic vessels revealed the presence of an angiocavernoma. Surgery took place on February 25th, 1999. Through a coronal interhemispheric approach, the angiocavernoma was reached and radically removed. The corpus callosum was carefully inspected, but no sign of involvement of the callosal fibers was found. The post-surgical course was marked by a regular, fast recovery of general functions, allowing MPT to be discharged from hospital two weeks after surgery. Four months later, a follow-up MRI (Fig. 1b) showed a residual lesion confined to the caudal portion of the right ACC (Broadman's areas 24 and 32). At that time the patient had completely recovered her ability to engage in normal daily activities.

Neuropsychological evaluation

The patient was first seen the day immediately before surgery (February 24th, 1999), and then re-assessed 4 months later (June 29th, 1999). The main findings from the psychometric assessment are summarized in Table I. The tests and scoring used, unless otherwise specified, refer to tests and normative data for the Italian population (20). Any score more than 1 standard deviation (sd) lower than the mean score of controls was considered pathological.

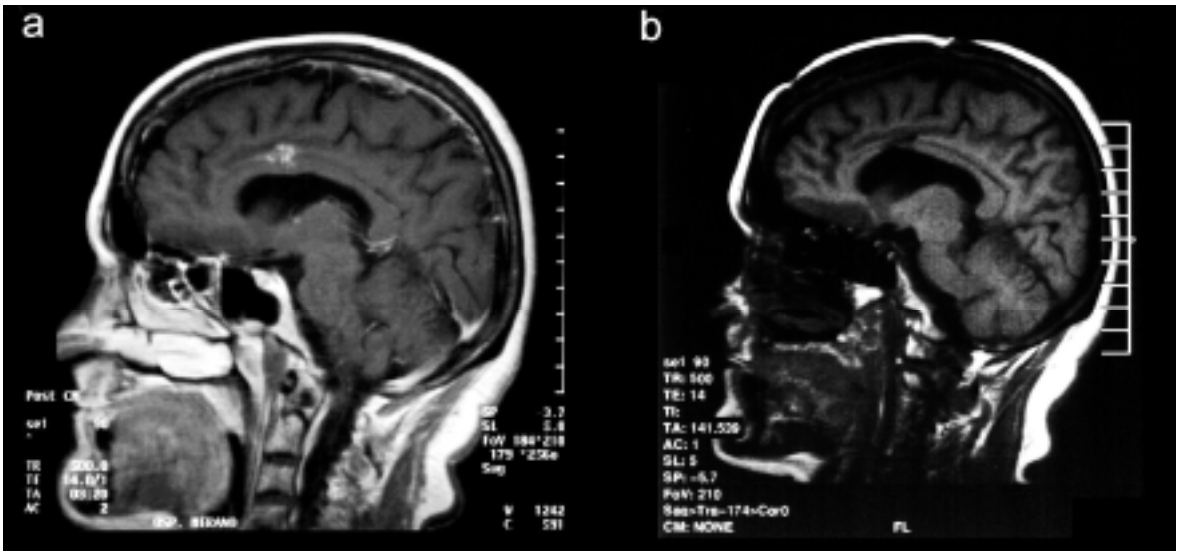

Figure 1 - Sagittal MRI scans. a) Pre-surgery T1-weighted scan with contrast medium showing a hyperintense signal in the right gyrus cinguli. The examination was performed on January 27th, 1999 at Merano City Hospital. b) Post-surgery T1-weighted scan without contrast medium showing a hypointense signal in the posterior part of the ACC. The examination was performed on June 26th, 1999 at Bolzano City Hospital.

Pre-surgery assessment

MPT showed good temporal and spatial orientation, and she was completely aware of her condition. No depression or any other instability of mood was recorded. The good performance (score=29; cut-off=23) on the Mini-Mental State Examination (MMSE) (21) demonstrated the complete preservation of her general intellectual abilities. Spontaneous speech, comprehension, repetition, reading, and writing were all normal. Visual perception and praxis, assessed by means of simple clinical, bedside tests, were also normal. Presented with the Visual Search Test, MPT started the barrage from the left upper corner, and detected all the target stimuli. Moreover, she did not show any tendency to miss the left-sided stimuli in the double bilateral stimulation condition, thus confirming the absence of visuo-spatial neglect or extinction. Left limb gestures in response to verbal command were extremely accurate, and MPT had no problems, while blindfolded, in naming everyday objects explored with her left hand, or in transferring somaesthetic information from one hemisphere to the other. Taken together, these results demonstrated the functional integrity of the callosal pathways.

By contrast, the following impairments were recorded. Despite demonstrating correct knowledge of arithmetic rules and the numbering system – the patient performed well on mental calculations from the Arithmetic Judgement Test – MPT was unsuccessful on the reverse numbering tasks both of the MMSE (progressive subtraction of 7 digits starting from 100: 93 – 80 – 83 – 70… I can't), and the Arithmetic Judgement Test (progressive subtraction of 3 digits starting from 20: 17 – 15 – 14 – 11 – 9 – 8 – 5 – 2). On the Verbal Fluency Test, which requires the subject to produce, within a time limit of two minutes, as many different words as possible that belong to a given semantic category (color, fruits, cities, and animals), MPT's score was more than 1 sd lower than the mean score of controls; furthermore, she also showed a certain tendency for perseverations. When asked to copy the Rey - Osterreith Complex Figure (22), MPT achieved a very low score, clearly the result of a disorganized approach to figure copying (Fig. 2a).

Other, peculiar, impairments were recorded on memory tests. Verbal and spatial span were within the normal range. Semantic knowledge, assessed by means of two 10-item questionnaires concerning animals' habits and famous people from Italian history, was fully preserved, as was retrograde memory, investigated by means of a 22-item questionnaire concerning events occurring between the year of the patient's birth and 1988 (23). Otherwise, MPT gave below normal range performances when tested for immediate recall of a list of 30 words which she had first been allowed to study for 5 minutes, and very poorly when required to pick out these 30 words when they were randomly inserted in a longer list of 60 words (24).

Finally, MPT was also unsuccessful on both the Corsi Block Tapping Test, and the Selective Reminding Test, which involve the learning of supraspan sequences, spatial and verbal, respectively. In the Corsi Block Tapping Test, the examiner taps eight blocks in a predetermined sequence, which the subject is required to copy. This is done repeatedly until the subject has reproduced the sequence correctly on three consecutive attempts; if the subject does not meet the criterion in 18 trials, the task is interrupted. An effective strategic approach to this task is the "chunking" of shorter, within span, sequences, which, serving as single memory units, are gradually put together to form the longer sequence. However, in all the trials, MPT instead attempted to reproduce the entire sequence of spatial positions, and thus failed to meet the criterion. In the Selective Reminding Test, patient is tested for immediate recall of a list of 10 words read aloud by the examiner at a rate of 1 word per 2 seconds. On all subsequent trials, the examiner reminds the subject only of the items that were omitted on the immediately preceding trial. It follows that, in order to meet the criterion, the patient, starting from the second trial, has to maintain within his/her working memory words already remembered, and words generated by the examiner. In all the trials, MPT promptly reported most of the items just presented by the examiner, but only very few of the items previously learned, thus recording a very low score.

Table I - Main findings from psychometric assessment.

		Assessment		Normative data	
		Pre-surgery	Post-surgery	Mean	sd
		raw scores			
Mini Mental State Examination		29	28	cut-off = 23	
Verbal Fluency Test		13*	15.5	18.03	± 4.69
Copy of Rey Complex Figure		22*	23*	32	± 1.80
Word list test	immediate recall	10*	11*	13.3	± 2.12
	delayed recognition	9*	16*	26.6	± 3.07
Corsi's Block Tapping Test		13.18*	16.66	20.88	± 5.10
Selective Reminding Test	recall from long-term memory	31*	73*	122.05	± 31.90

* Below 1 sd of controls' average. Both the psychometric assessments were performed at the Hospital of Bolzano, on February 24th, 1999 (Pre-surgery), and June 29th, 1999 (Post-surgery), respectively.

Post-surgery assessment

Neuropsychological follow-up assessment four months after surgery revealed an improvement in the patient's performance on several tests (Table I). In particular, the scores achieved on single trials from both the Corsi Block Tapping Test and the Selective Reminding Test, were consistently greater in the post- than in the pre-surgery condition (Wilcoxon matched-pairs signed-ranks test $p<0.05$, and $p<0.001$, respectively). A significant improvement was also recorded on the delayed recall task (pre-surgery: 9 correct answers out of 30; post-surgery: 16 correct answers out of 30, Fisher exact probability test: $p<0.05$), but not on the immediate recall task (pre-surgery: 10 correct answers out of 30; post-surgery: 11 correct answers out of 30, Fisher exact probability test: n.s.) from the word list test. However, it is noteworthy that, in spite of these improvements, the patient's performance still remained well below normal range on both the delayed recognition task from the same word list test, and the Selective Reminding Test. Moreover, patient's copy of the Rey Complex Figure was still fragmented (Fig. 2b), and she was again unsuccessful on the reverse numbering tasks from both the MMSE (100 – 93 – 80 – 83 – 70… I don't know) and the Arithmetic Judgement Test (20 - 17 – 14 – 12 – 9 – 7 – 4 - 2). Taken together, these results demonstrated the persistence of a mild impairment of executive functions.

Discussion

As pointed out by Smith and Jonides (25), "there is lack of consensus about a taxonomy of executive functions". Nevertheless, it is generally acknowledged that they involve: focusing attention on relevant issues and inhibiting irrelevant, interfering information, decision making, planning a sequence of processes to achieve goals and intentions, monitoring of ongoing behaviour, and shifting of strategies to adapt to changing circumstances (26). Several, different, standardized neuropsychological tests have been used to assess executive functions. However, all of these measures are multi-dimensional, i.e., they elicit multiple cognitive processes, and as a result, arguments for a specific impairment of executive functions are usually based on qualitative interpretations of the reasons for test failure, rather than interpretations of rough quantitative scores on specific tests.

In the present paper we report a longitudinal study of impairment of executive functions in a single patient with an ACC lesion due to the presence of an angiocavernoma located at the junction of the anterior third with the middle third of the right gyrus cinguli (Fig. 1a). An extensive neuropsychological evaluation carried out just before surgery demonstrated that the patient's overall level of intellectual functioning was well within the normal range, but the results of several, different tests suggested a significant impairment of executive functions.

Indeed, poor performance and repetitions on the Verbal Fluency Test, as well as errors in serial subtractions, clearly reflected problems in mental tracking, and, more generally, difficulty in doing more than one thing at a time (e.g., keeping track of words already said while searching her vocabulary for other words). MPT's failure on Corsi's Block Tapping Test probably depended on deficits in self-monitoring (to avoid repeating ineffective responses), and shifting strategies (to change behavior in order to meet the task criterion). It is noteworthy that defective monitoring of performance, and defects in the choice of strategy applied to cognitive tasks have been taken as the most direct evidence of an impairment of executive functions (27,28). Given the complexity of the design, successful copying of the Rey Complex Figure depends on the construction of a systematic plan of action at the start. Thus, although visuospatial disorders may also disrupt performance, a poor response to this task is believed to be due to deficient

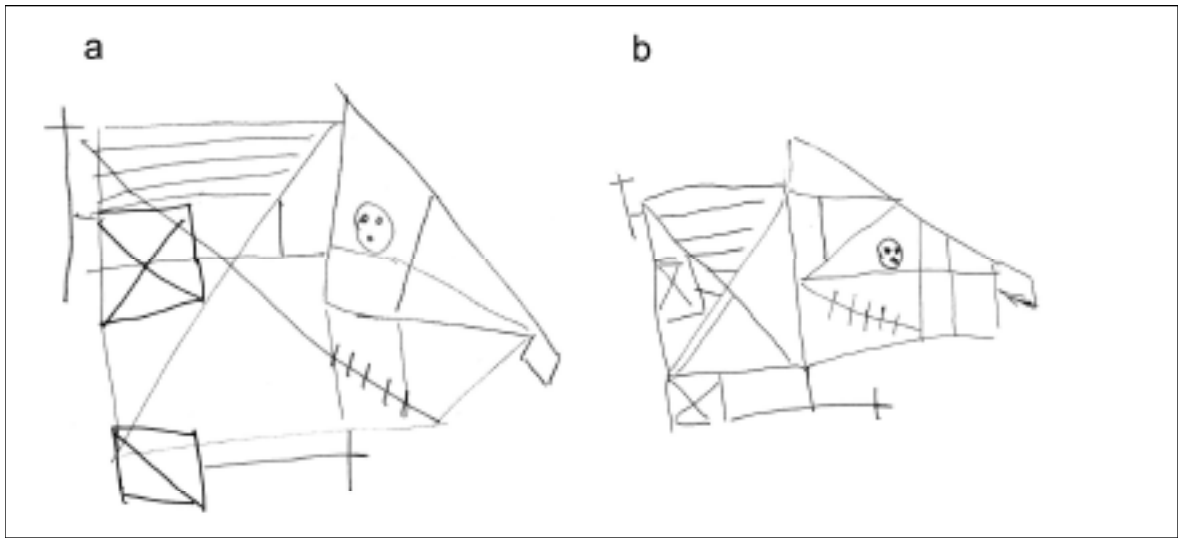

Figure 2 - MPT's performance on the Rey - Osterreith Complex Figure copying test: one day before surgery (a), and four months after surgery (b).

planning behavior (22). MPT's haphazard, fragmented copy of the Rey Complex Figure (Fig. 2a) probably reflects difficulty constructing and implementing a sensible plan of action. Finally, on both the delayed recognition task, and the Selective Reminding Test, MPT showed an exaggerated susceptibility to retroactive interference which meant that the presentation of different words made her unable to recall those already stored in her long-term memory (see Table I).

Four months after surgery, a follow-up MRI examination showed a lesion confined to the most caudal portions of Broadman's areas 24, and 32 within the right ACC (Fig. 1b). Supporting the argument that limited lesions in the ACC result in limited cognitive changes, which tend to resolve in a brief period of recovery (16,29), neuropsychological re-assessment at that time demonstrated a marked improvement in the patient's performance on several executive function tasks. Nevertheless, MPT was still unsuccessful on serial subtraction tasks, and copying the Rey Complex Figure, and achieved a very poor score on the delayed recognition task, and the Selective Reminding Test, thus suggesting that focal lesions in the ACC may lead to a persistent, mild impairment of executive functions. In particular, it seems that brain lesions that encompass the most caudal portions of ACC do exacerbate interference from competing stimuli, further corroborating the idea that ACC is critical for monitoring interference between competing information processing pathways.

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References

1. Vogt BA, Finch DM, Olson CR. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. Cereb Cortex 1992;2:435-443
2. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. Brain 1995;118:279-306
3. Bates JF, Goldman-Rakic PS. Prefrontal connections of medial motor areas in the rhesus monkey. J Comp Neurol 1993;336: 211-228
4. Pardo JV, Pardo PJ, Janer KW, Raichle ME. The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. Proc Natl Acad Sci USA 1990;87:256-259
5. Baker SC, Rogers RD, Owen AM et al. Neural systems engaged by planning: a PET study of the Tower of London task. Neuropsychologia 1996;34:515-526
6. Barch DM, Braver TS, Sabb FW, Noll DC. Anterior cingulate and the monitoring of response conflict: evidence from an fMRI study of overt verb generation. J Cogn Neurosci 2000;12: 298-309
7. Klingberg T, O'Sullivan BT, Roland PE. Bilateral activation of fronto-parietal networks by incrementing demand in a working memory task. Cereb Cortex 1997;7:465-471
8. D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M. The neural basis of the central executive system of working memory. Nature 1995;378:279-281
9. Cowell SF, Egan GF, Code C, Harasty J, Watson JD. The functional neuroanatomy of simple calculation and number repetition: a parametric PET activation study. Neuroimage 2000;12:565-573
10. McIntosh AR, Grady CL, Haxby JV, Ungerleider LG, Horwitz B. Changes in limbic and prefrontal functional interactions in a working memory task for faces. Cereb Cortex 1996;6:571-584
11. Barch DM, Braver TS, Nystrom LE, Forman SD, Noll DC, Cohen JD. Dissociating working memory from task difficulty in human prefrontal cortex. Neuropsychologia 1997;35: 1373-1380
12. Botvinick MM, Nystrom L, Fissel K, Carter CS, Cohen JC. Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature 1999;402:179-181
13. Braver TS, Barch DM, Gray JR, Molfese DL, Snyder A. Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. Cereb Cortex 2001;11: 825-836
14. Whitty CW, Lewin WA. A Korsakoff syndrome in the post-cingulectomy confusional state. Brain 1960;83:648-653
15. Cohen RA, Kaplan RF, Moser DJ, Jenkins MA, Wilkinson H. Impairments of attention after cingulotomy. Neurology 1999;53: 819-824
16. Janer KW, Pardo JV. Deficits in selective attention following bilateral anterior cingulotomy. J Cogn Neurosci 1991; 3:231-241
17. Laplane D, Degos JD, Baulac M, Gray F. Bilateral infarction of the anterior cingulate gyri and of the fornices. Report of a case. J Neurol Sci 1981;51:289-300
18. Turken AU, Swick D. Response selection in the human anterior cingulate cortex. Nat Neurosci 1999;2:920-924
19. Danckert J, Maruff P, Ymer C et al. Goal-directed selective attention and response competition monitoring: evidence from unilateral parietal and anterior cingulate lesions. Neuropsychology 2000;14:16-28
20. Spinnler H, Tognoni, G eds Standardizzazione e Taratura Italiana di Test Neuropsicologici. Ital J Neurol Sci 1987 (Suppl 6)
21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198
22. Osterrieth PA. Le test de copie d'une figure complexe. Archives de Psychologie 1944;30:206-356
23. Andreani O, Amoretti G, Baldi P. MLT '88 Test di Memoria di Eventi Storici. Florence; Organizzazioni Speciali 1988
24. Peru A, Fabbro F. Thalamic amnesia following venous infarction: evidence from a single case study. Brain Cogn 1997;33:278-294
25. Smith EE, Jonides J. Storage and executive processes in the frontal lobes. Science 1999;283:1657-1661
26. Stuss DT. Contribution of frontal lobe injury to cognitive impairment after closed head injury: Methods of assessment and recent findings. In: Adams RL, Parsons OA, Culbertson JL, Nixon SJ eds Neurobehavioral Recovery from Head Injury. New York; Oxford University Press 1987: 166-177
27. Gagné RM Learning outcomes and their effects. Useful categories of human performance. American Psychologist 1984;39:377-385
28. Baddeley AD. Working Memory. Oxford; Clarendon Press 1986
29. Stuss DT, Floden D, Alexander MP, Levine B, Katz D. Stroop performance in focal lesion patients: dissociation of processes and frontal lobe lesion location. Neuropsychologia 2001;39:771-786