

Structural Changes in the Insular Cortex in Alcohol Dependence: A cross sectional study

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Objective: This study was conducted to determine the changes in the insular cortex in alcohol dependent subjects, and to compare the same with controls, the associated clinical findings.

Methods: The study group consisted of 30 subjects with alcohol dependence syndrome (ADS) selected randomly from the out patient services of the department of psychiatry of a tertiary care hospital. The control group consisted of 30 matched subjects selected randomly from the out patient department and from patients screened for uncomplicated headache. Both groups were examined by a computerized scan (CT), and Mini Mental Status Examination (MMSE).

Results: Chi square, and 't' test were done after calculating the Evan's ratio. The two groups were compared to assess the cortical atrophy and ventricular enlargement. Cognitive functions were tested by MMSE, and the scores were compared. Atrophy was significantly higher in the experimental group; however, it was not significant. Cognitive functioning was found to be significantly impaired in the experimental group.

Discussion: The study showed that alcohol dependence leads to cortical atrophy which is age independent. The statistically significant disturbance in the MMSE scores along with the frontal and parietal cortical atrophy is also indicative of the insular cortex involvement in the experimental group.

Conclusion: Alcohol dependence leads to cerebral atrophy along with the involvement of the insular cortex.

Keywords: Alcohol related disorders, Cerebral cortex, Cognition, Computed tomography

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The insular cortex is a cerebral cortical structure which lies deep within the lateral fissure in between the temporal lobe and the frontal lobe (1). The overlying cortical areas are the operculum which is formed from the parts of the enclosing frontal, temporal and parietal lobes. The insula plays a role in diverse functions usually linked to emotion or regulation of the body's homeostasis (2). These functions include perception, motor control, self-awareness, cognitive functioning, and inter personal experiences. Hence, it is implicated in the development of psycho pathology (3). Alcohol consumption is widespread in India. Prevalence of alcohol abuse in India is 6.9 per thousand with urban and rural rates being 5.8 and 7.3 per thousand respectively (4, 5).

CT scan is a widely available imaging technique that can detect gross neuropathological changes like cortical atrophy, ventricular enlargement, tumor, calcification, cerebrovascular disease. It is a reliable, economical, and effective imaging technique which can detect unsuspected neuropathological conditions (6). CT scan is a relatively simple technique which relies on the

Same physics as conventional x-ray; structures are distinguished from one another by their ability to absorb energy from x-rays. It, however, has some important disadvantages like exposure to ionizing radiation, limited visualization of structures in the transverse plane, relatively poor contrast between white and gray matter, poor visualization of posterior cranial fossa structures. Despite all this, CT scan is a useful technique for measuring intracranial structural changes (6). A number of functional brain imaging studies have shown that the insular cortex is activated when drug abusers are exposed to environmental cues that trigger cravings (2, 7). This finding has been shown for a variety of drug abuse, including cocaine, alcohol, opiates and nicotine (7). Despite these findings, the insula has largely been overlooked with regards to its role in drug addiction, perhaps because it is not known to be a direct target of the mesotelencephalic dopamine system which is central to current dopamine reward theories of addiction (8). To date, several researches have been done on the structural brain changes in alcohol dependence. Some have found frontal lobe change (9-12), others have

found parietal (13) or temporal lobe atrophy (14) or ventricular dilatation (15) but none has focused attention on the insular cortex. This study was conducted to address this lacunae in the literature and to determine the changes in the insular cortex and the associated clinical findings.

Materials and Method

The study was conducted at the Department of Psychiatry, Institute of Medical Sciences, Banaras Hindu University. The study was approved by the ethical committee of the institute. The study group consisted of 30 patients randomly selected from the out patient services of the department. The inclusion criteria consisted of subjects fulfilling the DSM-IV TR criteria for alcohol dependence, and age group of 21 to 40 years. Subjects having any past history of head injury or unconsciousness, any significant systemic illness (e.g., hypertension, diabetes, ischemic heart disease, cerebro vascular accident, epilepsy, tuberculosis etc.), any substance dependence or abuse other than alcohol, any other psychiatric illness were excluded from the study. Control group consisted of 30 age and sex matched patients selected randomly from out patient department who fulfilled the selection criteria of age being 21-40 years and not having any psychiatric or medical co morbidity and from patients screened for headache. A written informed consent was obtained from every subject in both groups. Thorough neurological examination was performed before selecting cases and controls. CT scan was performed in the department of radiology of institute of medical sciences, Banaras Hindu University using General electrical 4000i CT scanner which used 5mm axial

sections from Reid’s baseline to vertex. The CT scan pictures were analyzed by an expert radiologist on the following parameters: (a) cortical atrophy (sulcal widening) was rated on four point scale for five cortical areas (frontal, parietal, occipital, temporal and insular) and a cumulative cortical atrophy score for the separate regions to give a possible maximum of 20. (b) Evan’s ratio was measured as the ratio between frontal horns of lateral ventricle to the maximum internal skull diameter. Evan’s ratio is more reliable than ventricular measurement alone(16).Mini Mental Status Examination (MMSE) was administered using the 30 point scale in order to assess the cognitive function of the experimental and control groups (17). The results were analyzed using the SPSS software for windows (version 13). The groups were analyzed by comparing the scores using a ‘t’ test and a chi square test; significance was fixed at less than.001.

Results

Majority of the study subjects in both groups belonged to 36 to 40 years group (43.3 and 36.7%) respectively. The majority of the subjects had alcohol dependence of more than 4-6 years duration (25 subjects, 83.3%). All the subjects were male (Table 1). Subjects with alcohol dependence had significantly higher mean cortical atrophy scores compared to control group. There was a great significant difference in the mean Evan’s ratio between the two groups (Table 2). The cumulative cortical atrophy score in the insular area was significantly higher compared to control group, and the difference was statistically significant (Table 3). There was a positive correlation between age and cortical atrophy between duration of illness and cortical atrophy, but correlations did not reach statistical significance. The correlations between Evan’s ratio and age, and also Evan’s ratio and duration of illness were

Table 1: Age distribution in the study and control groups

Age group (in years)	Study group (N=30)		Control group (N=30)	
	No.	%	No.	%
21-25	4	13.33	7	23.3
26-30	5	16.67	6	20
31-35	8	26.67	6	20
36-40	13	43.33	11	36.7

Table 2: Comparison of cortical atrophy score in study and control group

Range of cortical atrophy	Study group			Control group			t	p
	N=30	%	Mean ± SD	N=30	%	Mean ± SD		
0-2	12	40	1.58 ± 0.515	24	80	1.58 ± 0.717	0	>0.05
3-4	13	43.4	3.46 ± 0.519	6	20	3.0 ± 0.0	3.207	<0.01
5-6	5	16.6	5.20 ± 0.447	-	-	-	-	-
Mean cortical atrophy score	30		3 ± 1.414	30		1.867 ± 0.860	3.75	<0.01
Mean Evan's ratio	30		23.7 ± 2.44	30		27.83 ± 0.87	-8.743	<0.01

Table 3: Comparison of cumulative atrophy score in different areas of brain in study and control group

Cortical atrophy score in different areas of brain	Study group (N=30)		Control group (N=30)		t	p
	Cumulative score	Mean±SD	Cumulative score	Mean±SD		
Frontal	22	1.13 ± 0.629	15	0.67 ± 0.80	2.51	>0.05
Parietal	24	1.0 ± 0.525	13	0.70 ± 0.70	1.874	>0.05
Temporal	3	0.10 ± 0.31	0	0.0 ± 0.0	1.795	>0.05
Occipital	3	0.10 ± 0.31	5	0.17 ± 0.38	-0.75	>0.05
Insular	32	1.1 ± 0.71	20	0.62 ± 0.78	1.96	<0.01

Table 4: Comparison of mean Evan's ratio in relation to age between study and control groups

Age group (in years)	Evan's Ratio				t	P
	Study group (N=30)		Control group (N=30)			
	No.	Mean±SD	No.	Mean±SD		
21-25	4	23±1.41	7	28.43±0.976	-7.592	<0.01
26-30	5	23.4±3.2	6	27.67±0.52	-3.24	<0.05
31-35	8	23.5±3.07	6	28.167±0.75	-3.608	<0.01
36-40	13	24.15±2.12	11	27.36±0.81	-4.735	<0.01

Table 5: Comparison of MMSE Score between study and control groups

	CASE		CONTROL		p
	Total score	Mean	Total score	Mean	
MMSE	881	29.37±1.06	734	24.46±2.20	>0.05
Orientation	300	10±0	300	10±0	-
Immediate recall	90	3±0	86	2.87±0.12	>0.05
Recall after five minutes	87	2.9±0.11	40	1.33±0.43	<0.01
Attention- Concentration	150	5±0	96	3.2±0.32	<0.01

positive, but were statistically non significant (Table 4). The difference of the cumulative MMSE score between cases and controls was statistically significant as scores of attention and concentration (to utter individual words of W-O-R-L-D backwards) and recall of three unrelated objects after five minutes.

Discussion

Our study found that the majority of the subjects from the experimental group belonged to the age range of 36-40 years, and all the respondents were male, this finding is in accordance with the national prevalence shown in the other study groups(18). The incidence of alcohol dependence in men and women in India is 11.7 and 1.9 per thousand respectively (18). Most of the studies conducted in India indicate that alcohol dependence is widely prevalent in adolescents and adult males and <5% women consume alcohol .The adolescent group was not significantly affected in our study. Patients with duration of illness >6 years constituted the majority (60%). This was followed by >4-6 years (26.67%) this is primarily because most of the subjects reported seeking treatment for their alcohol dependence after a significant time lapse of 5 to 6 years(4).The experimental group had higher cerebral atrophy and ventricular enlargement along

with cognitive disturbances indicating the involvement of the insular cortex. In our study, statistically significant cortical atrophy was prominent in all the age groups of the study population compared to control group. The mean Evan's ratio did not show any definite pattern with duration of illness. As the correlation between cortical atrophy/ Evan's ratio and age/ duration of illness were statistically non significant, it can be safely concluded that the atrophic changes specific to insular cortex, are not dependent on age or duration of alcohol intake, but specific to alcohol dependence; this finding is in concordance with another study (19).

Alcohol dependence leads to multiple electrophysiological(20,21) ,anatomical (19),radiological(22) and blood flow changes in the brain(23).Our study also found evidence of atrophy ,although the evidence was not statistically significant , the trend was towards a higher atrophy in the experimental group compared with the control group. We found evidence of significant cortical atrophy in 60% of our alcohol dependent group ;and of them, a few had evidence of parietal atrophy and some had frontal cortical atrophy; this finding is similar to the findings of another study(19).The above changes lead to multiple cognitive deficits in terms of processing ,registering and recalling information which have been shown in a study that

elaborated multiple cognitive deficits can be used as a marker for alcohol dependence(24).An important study which used Positron Emission Tomography(PET) scan, found reduced cerebral metabolic rate for glucose bilaterally in the medial frontal area in alcohol dependent patients(25).The evidence from these studies lead researchers to suggest that the presence of electrophysiological deficits even in absence of apparent structural damage may possibly indicate the occurrence of neuro chemical or subtle morphological changes which may or may not be detectable by CT Scan but might reflect the imminent onset of overt structural change(25,26). Later studies clearly showed that chronic alcoholism leads to increase in density of NMDA receptors, particularly in frontal cortex which is largely responsible for neurotoxicity (27).These studies are a pointer to the structural damage that occurs in alcohol dependence subjects.

Our study found that the ventricular enlargement was much more in the experimental group than in the control group, though it was not statistically significant; however, this could be attributed to the small sample size. A similar observation has been reported by another study that showed ventricular enlargement to be a consistent finding in alcohol dependence and it increased with age (19).The same study also showed that ventricular enlargement was not significant in comparison with cortical atrophy, which was prominent and significantly related to age. Our study showed a different trend which could be attributed to the different age groups studied in the two studies(26-62 year age group as compared to 21-40 year age range in our study)(19). The difference in Evan's ratio as observed by our study has been found by another study (9) in contrast with Maes and his group who studied Evan's ratio in 47 alcohol dependent patients and 10 healthy volunteers but did not find any statistically significant difference between the two groups (6).

A model proposed by Naqvi et al.(7) states that the insula stores a representation of the pleasurable interoceptive effects of drug use (e.g. the airway sensory effects of nicotine, the cardiovascular effects of amphetamine), and this representation is activated by exposure to cues that have previously been associated with drug use. A number of functional imaging studies have shown that the insula is activated during the administration of drug abuse, or during exposure to drug cues, and this activity is correlated with subjective urges. Therefore, rather than merely representing the interoceptive effects of drug use , the insula may also play a role in memory for the pleasurable interoceptive effects of past drug use, anticipation of these effects in the future, or both. Such a representation may give rise to conscious urges that have a subjective feeling. We tried to asses the changes in the insular cortex as the right anterior insular region regulates the interaction between the selective attention created to achieve a task (the dorsal attention system) and the arousal created to keep focused upon the

relevant part of the environment (ventral attention system). This regulation might be particularly important during challenging tasks where attention might be fatigued and so cause careless mistakes. However, if there is too much arousal, it risks creating poor performance by turning it into anxiety (7). These findings are consistent with our finding of alcohol dependent subjects having significantly higher attention deficit than control subjects which was shown by the MMSE scores and their correlation among the experimental and control groups.

The results of the present study show intracranial structural changes in alcohol dependent subjects, particularly in cortical atrophy and Evan's Ratio. Our study did not attend to other parameters which are mentioned in the literature as they were out of the purview of our study. Future studies should consider other methods to establish the findings in the literature. Other advanced methods like MRI and blood flow studies would be more helpful. The study sample was very small, and a larger sample would be helpful in making robust conclusions. This study provides structural evidence for cognitive function impairment which occurs as a result of alcohol intake. This should extrapolate to early interventions to control alcohol dependence syndrome.

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