Olfaction & Limbic-Prefrontal Compromise Through the Course of Psychosis: What do Smell Deficits tell us about Disordered Adolescence?

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Syndromes of Schizophrenia (Liddle, 1987)

Psychomotor Poverty Syndrome	Disorganisation Syndrome	Reality Distortion Syndrome
Poverty of speech; Flatness of affect Decreased spontaneous movement	Disorders of the form of thought Inappropriate affect	Delusions Hallucinations
Impaired abstract reasoning Impaired long-term memory	Poor concentration Impaired ability for new learning	Poor performance in figure-ground perception.
Dorsal prefrontal cortex	**Orbital prefrontal cortex**	**Medial temporal lobe**

Background: Fronto-Limbic Networks Implicated in Psychosis

- Known difficulty framing heterogeneous array of symptoms & cognitive deficits found in psychosis
- Neurobiological findings implicate compromise of fronto-limbic networks (subcortical regions, medial-temporal & frontal lobes)

Behavioural Syndromes of Schizophrenia (Harvey, Curson, Pantelis et al, 1996)

Thought Disturbance	Social Withdrawal	Depressed Behaviour	Anti-social Behaviour
Incoherence of speech	Little spontaneous communication	Depression	Hostility
Odd/inappropriate conversation	Poor self care	Suicidal ideas or behaviour	Socially unacceptable habits
Poor attention span	Slowness		Destructive behaviour
	Underactivity		

Fronto-Limbic Networks & Psychosis: Framing a Research Paradigm

- Neuropsychological approach of comparing patterns of performance on cognitive tasks across neurological groups.
- These patterns may be utilised as a template to guide further explore similar, though attenuated patterns of performance in schizophrenia
- Challenge to identify relatively discrete probes/dissociative patterns enabling guided exploration of functional integrity of this circuitry

Windows the to Mind? Previous Olfactory Research

- Clinical observations triggered investigation of integrity of olfactory function (Edwards, Personal communication 93)
- Robust literature suggesting males with schizophrenia suffered olfactory agnosia in the presence of intact acuity
- Similar pattern also found in Wernicke-Korsakoff psychosis, implicating DMN of thalamus (Potter & Butters, 80)

University of Pennsylvania Smell Identification Test (UPSIT)

- Tests smell identification
- 40 multiple choice questions
  - Scratch panel, sniff and identify
- Standardised (age/gender)
  - Normosomnia scores
    - Male – 34-40
    - Female – 35-40
- Testing left and right nostrils (20 qs each)

Implications of Olfactory findings on Neurodevelopment

- Exploring neurodevelopmental hypothesis, olfactory identification deficits also found in 74 neuroleptic naïve first-episode patients (F=11.68, p<.001)=> stable at 6/12 follow-up (Brewer et al, Am J Psychiatry, 2001)
- Associations also found between olfactory identification ability & negative symptoms in this group (r=-.35*) *plus* no association with MTL tasks of new learning (similar to chronic group)

Previous Olfactory Research: Utility of Framing Hypotheses within a Broader Paradigm

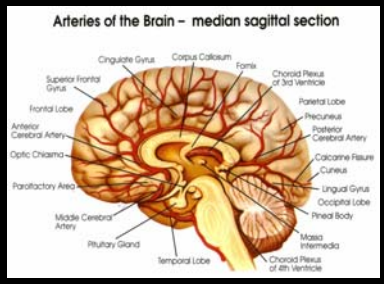
- OFC also relevant to olfactory identification ability (Zatorre et al 92)
- Previous study confirmed deficit (t = -3.22, p< .001) & found relationship (r=-.47*) b/w olfactory identification & negative symptoms in chronic group (n=26) cf. controls (n=19) (Brewer et al, Biol Psych , 96)

Olfaction & Psychosis: Can we utilise principles of olfactory function to track aetiology?

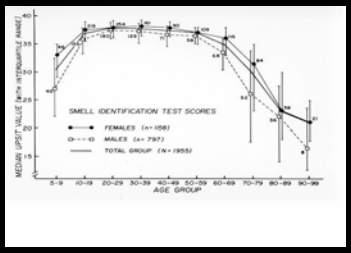
- Hierarchical progression of functional ability follows neural network from limbic system to PFC, paralleling increase cognitive load
- Identification ability parallels PFC development through adolescence
- Olfactory Processing is highly lateralised
- Generalised organic conditions compromise a range of olfactory functions

Melbourne Olfactory Research: Revealing a Consistent Story in Chronic & First-Episode Psychosis

- Previous study also found relationship (r=.56*) b/w olfactory identification & performance on executive (MWCST -Cat's) rather than memory tasks
- However memory & olfaction were associated (r=.51*) in controls (Brewer et al, Biol Psych , 96)
  - => Implicating PFC cf. MTL?



UPSIT Ability Reflects PFC Development



Previous Research: Tracking down Locii of Aetiological Compromise

- Olfactory identification deficits may serve as genetic markers or indicators for psychosis onset, or may be trait markers for poor prognosis
- Neurodevelopmental hypothesis would predict the presence of such olfactory identification deficits prior to illness onset (developmental vulnerability/ arrest?)
- No previous study had examined olfactory & related cognitive deficits in subjects at high risk for psychosis

Previous Relevant Olfactory Research

- Olfactory deficits not explained by acuity decrements or other peripheral factors
- Olfactory problem stable at 6-month follow-up
- Olfactory identification deficits implicate orbito-frontal aspects after accounting for other factors

Method: Subjects

- 31 (71.0 %M) comparison subjects (CTL)
- 81 (56.7 % M) subjects at high risk for psychosis (HR)
  - Consecutive referrals to Personal Assessment & Crisis Evaluation (PACE) clinic: Melbourne, Australia
  - SELECTION CRITERIA: 'Specific state' risk factors
    - Attenuated psychotic symptoms detectable but sub-threshold
      - delusions, hallucinations, thought disorder (48.1%)
    - Transient psychotic symptoms =>likely to make transition due to mental state changes, where psychotic symptoms resolve within 1 wk (11.1%)
    - Trait plus state risk factors: History of 1st degree relative with any psychotic disorder or schizophrenia spectrum Axis II plus prodromal mental state (13.6%)

MELBOURNE HIGH RISK STUDY: OLFACTORY IDENTIFICATION ABILITY IS IMPAIRED IN INDIVIDUALS AT ULTRA-HIGH RISK FOR PSYCHOSIS WHO LATER DEVELOP SCHIZOPHRENIA

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Method: Subjects / Measures

- 22 (27.2%) of **HR** patients developed psychosis in 18 months from referral
- 12 (54.5%) received Schizophrenia/form diagnosis
- 2 major depression with psychotic features
- 1 schizoaffective (depressed)
- 3 bipolar disorder
- 1 substance induced psychosis
- 3 psychosis NOS

Method: Measures

- Cognition:
  - Premorbid IQ (NART): COGMAPS
- Olfaction:
  - University of Pennsylvania Smell Identification Test (UPSIT)
- Psychopathology:
  - SCID-IV, BPRS, SANS

Discussion: Olfaction in UHR

- Olfaction examined for first time in unique cohort
- Olfactory identification deficit specifically in patients who develop Scz/Sfrm psychosis c.f. all other UHR-P groups
- No association b/w UPSIT & age in UHR-P, though it did exist in UHR-NP group

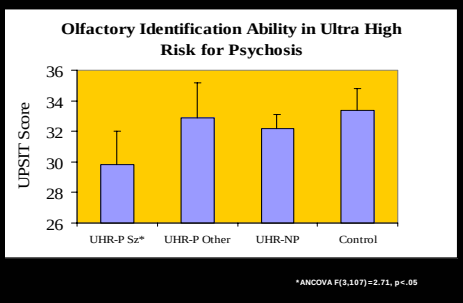
Results: Subject Characteristics

	UHR-P (n=22)	UHR-NP (n=59)	CTL (n=31)
Age	19.9 (4.1)	20.4 (3.2)	21.1 (3.9)
Premorbid IQ	99.9 (12.8)	100.5 (13.0)	108.5 (9.7)**
BPRS	20.0 (5.5)	19.6 (8.8)	
SANS	28.0 (20.2)	22.4 (16.5)	
UPSIT	31.2 (1.6)	32.2 (0.9)	33.4 (1.4)^

** p < .01; ^controlling for NART IQ

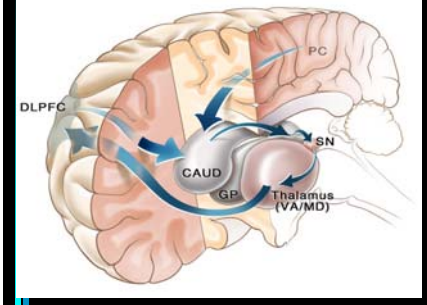
Discussion: Future Directions

- Next phase is to follow up the psychotic UHR-P group to examine impact of developmental stage at illness onset & impact of further brain changes
- Findings might implicate compromise of prefrontal function, where the onset of schizophrenia leads to arrest of normal development of olfactory ability
- Findings consistent with other neuropsychological & neuroimaging work (Pantelis et al a & b)



Discussion: Implications

- Decline in performance may be occurring during transition to frank psychosis in Scz group given previous findings in FE psychosis group, but consider structural imaging findings that reflect less stable picture?
- Findings may be associated with OFC changes over the transition period/OFC developmental vulnerability



From the primal brain stem to the human frontal cortex: Limbic Interplay between thought & reflex

Neurological Dissociation of Olfactory Function

- Olfactory acuity deficits implicate MTL circuitry (Raush & Serafitinides 75) where lobectomy may disconnect primary olfactory processing (acuity) areas from higher order processing (identification) (Jones-Gotman et al 77)
- Neurological deficits suggest hierarchical olfactory processing pattern from thalamic DMN to temporal (entorhinal) cortex, & then to lateral posterior OFC (Potter & Butters 80)

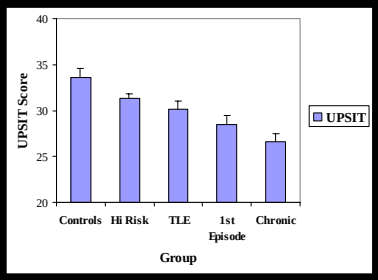
Implications of Olfactory deficits: Tracking neuro-developmental arrest vs. prefrontal compromise

- Does arrest of OI implicate neurodevelopmental arrest in other disorders mediated by OFC function?
  - Autism/Asperger's: Implicates OFC compromise (Bradshaw & Shepherd, 2000/; with disruption of association with age in young HFA subjects (Brewer et al, In submission) & OI deficits in Asperger's; Suzuki et al; 2003
  - ADHD: Implicates OFC compromise (Hesslinger et al, 2002; Sowell, 2003) Biological vs Behavioral (aggressive) subtype? (Karsz, Brewer, Anderson et al)
  - Conduct Disorder/Borderline Personality Disorder: Aggressive subtypes implicate OFC (Davidson et al, 2002) Biological vs behavioral subtypes? (Nudds, Brewer et al)
  - OCD: Structural & functional OFC abnormalities (Rauch et al, 1997) => OI Deficits (Barnett, Maruff, Purcell, Wainwright, Kyrios, Brewer & Pantelis 1999)

Neurological Dissociation of Olfactory Function (cont)

- Recognition, discrimination & short-term memory relies upon integrity of these pathways (especially on right) & deficits increase as area of compromise passes more anteriorly into OFC
- Prefrontal lesions result in more dramatic olfactory deficit than midline thalamic damage alone=> if OFC is spared, identification is intact, if not, identification but not acuity deficits are present (Jones-Gotman & Zatorre 88)

Comparison of Olfactory Identification x Group



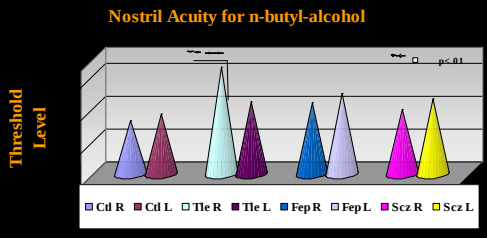
MNC/EPPIC/MHRI/St V's Olfactory Research

- Hypotheses:
  - TLE patients will demonstrate reduced acuity cf. FEP & SCZ
  - SCZ patients will demonstrate impaired identification cf. TLE
- Threshold Detection:
  - 10 increasing concentrations from 1 x 10^{-5} to 2M *n*-butyl-alcohol in distilled H_2O) presented mono-rhinally in plastic capped test tubes (higher score=> less acuity ability)

MNC/EPPIC/MHRI/St V's Olfactory Research

- Results:
  - No laterality differences in acuity for CTL (n=38), FEP (n=40), or SCZ (n=50) Right nostril acuity significantly worse than left (7.21[1.8]) in TLE (n=29: 41%Male), (F[1,18]=3.3, p<.04) not explained by lesion side or gender.

Group x Nostril Comparisons for Olfactory Threshold



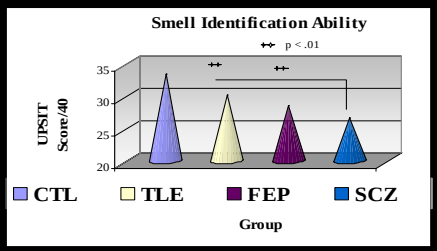
MNC/EPPIC/MHRI/St. V's Olfaction Results

- TLE acuity (8.3[1.6]) significantly worse than SCZ (7.0[2.3]) & CTL (6.6[2.3]) for right nostril only, not explained by age, sex, smoking, verbal memory or IQ
- Acuity not related to identification ability across all groups, but is related to verbal recall (RAVLT) in CTL (r=-.44*) & WMS-R Global Memory Index (r=-.51*) in TLE (Left nostril)
- Identification ability poorer in TLE cf. CTL & significantly better than SCZ. No effect of lesion side, age, smoking or premorbid IQ, however females were significantly higher (31.65[3.6]) than males (27.91[5.4]), & significant effect of verbal memory (VMI: F(1,105)=18.1, p<.001)

Related Pheromonal Research

- Strange odour in sweat suggests metabolic error (Smith & Sines, 1960) which may weaken during remission
- Patients with schizophrenia have reduced androstenol levels in urine- especially young males (Brooksbank & Pryse-Phillips, 1964)
- Urinous odour also stored in male fatty tissue, plasma & axillary sweat from steroid (androstenone) (Kloek, 1961; Claus & Alsing, 1976; Gower, 1972)
- Odourous substance in schizophrenia identified as trans-3-methyl-2-hexanoic acid (Smith et al, 1969)
- Males have increased acuity for androstenone => Based on Weiner's hypothesis of habituation in presence of reduced secretion (Bradley, 1984)

Group Comparisons of Olfactory Identification



Acuity Research in Schizophrenia

- Not different to CTL's in androstenone detection (Isseroff et al, 1987)
- Intact acuity for *n*-butyl-alcohol & No difference b/w M & F (Kopala et al. 1989)
- Higher thresholds in negative cf. positive symptom subgroup for musk ketone; CTL cf. SCZ? NS (Geddes et al, 1991)

AIMS:

- Examine incidence of acuity for pheromones in psychosis
- Synthesise Hexanoic Acid derivative & examine acuity for this substance across groups

Acuity in Psychosis Study: MNC/MHRI Method

Subjects:

* Thirty-one (FE) patients followed up from EPPIC
* Twenty-four age- & NART-matched Controls (CTL)
* Thirty-two Chronic Schizophrenia patients (CHR)

Measures:

* COGMAPS, Acuity (Threshold Dectection), UPSIT as in previous reports
  - Hexanoic acid derived by synthesising trimethyl phosphono- acetate & 2-pentanone => 8 levels in odourless methanol

* Steroid Detection:
  - Forced choice (Yes/No) to 5-alpha-16-en-3-one (25mg), estrone-3-sulfate (100 mg) & androsterone sulphate (25 mg)

Results

	CTL n=24	FE n=31	CHR n=32
UPSIT/40	33.5 (2.9)	30.3 (4.8)*	26.0 (6.8)**
Detection: (% yes)			
Androstenone 16	44.7	35.7	32.8
Androsterone-Sulphate	34.2	42.9	34.4
Estrogen Sulphate	31.6	31.0	31.1
Butanyl Threshold/10:			
Left Nostril	6.83 (2.3)	7.47 (2.1)	7.3 (2.0)
Right Nostril	6.63 (2.3)	7.12 (1.8)	7.0 (2.4)
Hexanoic Acid Threshold/8	3.3 (2.0)	3.7 (1.5)	4.9 (2.2)**

Results

	CTL n=24	FE n=31	CHR n=32
Age	20.21 (4.19)	22.94 (3.9)	33.13 (8.4)**
% Male	79.2	74.2	87.5**
NART IQ	106.4 (9.3)	102.0 (12.3)	103.9 (13.0)
Years Smoked	1.88 (3.3)	5.75 (5.7)**	12.1 (5.7)**
Cigarettes/Day	10.63 (6.6)	9.39 (10.2)	22.73 (14.7)**
Medication (%)	None	29.9	15.6
	Typicals	35.5	25.0
	Risperidone	29.0	0.0
	Clozapine	6.5	59.4

Results:

* No difference b/w groups in detection of Butanyl, NS trend for F to be more sensitive than M, however predominantly M sample
* Significantly reduced sensitivity to schizophrenia odour in CHR relative to FE & CTL's ($p < .01$)
* General trend for pheromonal anosmics to have reduced sensitivity to HA in all groups with significant difference in CHR ($p < .01$) only after bonferroni adjustment
* No group x pheromonal anosmia interaction effect for HA acuity

Results: (Mean; SD)

	FE n=31	CHR n=32
CPZ equivalent (mg/day)	84.80 (140.3)	482.07 (317.3)**
Manchester Total	16.00 (0.4)	12.47 (4.8)
Reality Distortion	2.50 (2.1)	3.95 (2.2)
Disorganisation	4.00 (0.5)	2.26 (1.8)*
Psychomotor Poverty	3.00 (0.8)	3.97 (2.3)
Diagnosis (%):		
Schiz/form	42.9	100.0
Affective	31.0	
Schiz-Aff	14.3	
Other	11.9	

Discussion:

- Use of HA has identified acuity deficits in CHR patients
- HA may be a more sensitive index of olfactory acuity in Scz than more traditionally used substances
- Acuity findings implicate MTL function => laterality value in TLE research & role for using dissociation from identification function to further clarify patterns of relationship between symptoms & cognition in Scz

IMPLICATIONS:

- => Genetic Research. Eg Kallman's Syndrome
- Fatty Acid Research/HA enzyme?

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