papers

Title: classification of first-episode SZ, chronic SZ & healthy-control(HC) based on brain network for MMN by graph-neural-network(GNN) [2021]

TERMS & ABBREVIATIONS:

- FESZ = First Episode Schizophrenia
- CSZ = Chronic Schizophrenia
- HC = Healthy Control
- GNN = Graph Neural Network
- CR = Critical Risk = Ultra-Hig Risk

Aim:

1. An in-depth invstigation in brain functional connectivity during MMN process among patients with **FESZ, CSZ, HC**
2. Based on brain functional connectivity found in 1., develop GNN tenary classifier of output classes FESZ, CSZ, HC

Experiment variables:

- 128 channel EEG
- 40 FESZ patients
- 40 CSZ patients
- 40 matched HC subjects

Points:

- The duration MMN may be more sensitive than the frequency MMN in differentiating between schizophrenia nad healthy subjects. *[Introduction, p2, s4-s7]*

Title: Auditory mismatch negativity in bipolar disorder: a focused review [2021]

Abstract

- cortical glutamatergic NMDA receptor activity and disturbance can be probed using audiotry MMN, of which MMN supports NMDA system involvement in the pathophysiology of schizophrenia and bipolar disorders.
- MMN can be considered a correlate of a common pathology of SZ and BD illnesses

Introduction

- there exists structural brain abnormalities and neuropsychological deficiencies in SZ and BD
- MMN can be sourced for Giard etal 1990, Naatanen etal 1990:
  - in the primary auditory cortex contralateral to the ear of simulation and
  - frontal cortex, mainly in the right hemisphere
- reduced MMN amplitude can be associated with loss of grey matter in the left superior temporal gyrus Salisbury etal 2007
- MMN deficit index cortical NMDA receptor dysfunction mostly affecting memory trace function and hence cognition Gene-cos etal 1999
- NMDA modulates the P3a ERP component Watson etal 2009
  - The P3a is an automatic process which is impaired in SZ Koshiyama etal 2020

Title: Neurophysiological biomarkers in schizophrenia - P50, mismatch negativity and TMS-EMG and TMS-EEG

> ### Aim
>
> - Updated overview of studies that have examined the potential of P50 and MMN to be used as endophenotypes and predictiver markers for interventions targeted at cognitive and psychosocial functioning

> ### Methods and Results
>
> - Increased P50 gating ratio(ratio of P50 to redundant auditory stimuli compared to original auditory stimuli) has been found in patients with schizohrenia
> - MMN is followed by tow EEG components P3a(peaks between 250-300ms) and RON(peaks between 400-500ms) which represent shifting of attention to oddball stimulus and reorientation of attention to detect further stimulus changes. P3a and RON have been shown to be impaired in patients with schizophrenia
>
> ***Characteristics of endophenotype & Predicitive Biomarker***
>
> - EEG microstates and slow wave oscillations have been proved to be candidates for shizophrenia endophenotypes EEG microstates, slow wave oscillations
> - MMN has good test-retest ability with high interclass correlation coeffficeints(ICC) SZ biomarker characterization
> - Evidence for MMN trait stability is mixed
> - Mixed results in frequency deviant MMN characterizing SZ illness duration.meta analysis of SZ/MMN disease progression, MMN in SZ meta analyis,fMMN
> - A work reports 63% and 68% MMN heritability for peak amplitude and mean amplitude respectively. heritability studies of MMN

- Another meta analyisis showed a trend for decrease in MMN amplitude in relatices of patientsmeta1 which was in agreement with another meta analysismeta2
- Another study demonstrates the intrinsic effect of deletion syndrome, a molecular risk factor of MMN, suggesting a potential genetic link. deletion syndrome

MMN as a predictive marker/ cognitive, psychosocial relationship

- MMN has been shown to consistently correlate with cognitive functioning, but pattern of correlation among different works have varied.
- dMMN and iMMN deviations are identifiable in the early stages of SZ, while fMMN become more prominent in later stages of the illness.grey matter deficits in MMN, dMMN, iMMN, fMMN pattern studies
- MMN can be a predictive marker when audio perceptual training processes are employed.MMN in perceptual learning
- Early auditory processing(EAP) measurement using MMN, P3a and RON might be directly associated with comprehensive assessment of cognitive functioning.EAP & cognitive functioning
- peak amplitude of MMN could acoount for variation of perfromances in daily tasks.daily functioning
- MMN current density values might predict patient improvement over course of social skills training. MMN-social_skills prediction

Discussion

- moderate test-retest reliabilty
  mixed findings in heritablility, trait stability and diagnostic specificity of MMN
  consistent correlation between MMN and cognitive task performance
  MMN predictive of performance in auditory perceptual training exercises

Mismatch Negativity Predicts Remission and Neurocognitive function in Indivivuals at Ultra-High Risk for Psychosis

Aim

- Investigating whether dMMN or fMMN could predict prognosis, remission and neurocognitive functioning in individuals at UHR

Methods

- 24 UHRs, 18 HCs
- remission defined as functional and symptomatic improvement after 180 days using GAF and SOPS scores
- Neurocognitive function measured using BACS
- baseline MMN amplitude comparision betwwen remitters and non-remitters

- Multiple regression analyses for identification of predictors for functioning, positive symptoms and neurocognitive function
- baseline coorection by subtracting mean amplitude from -100ms to 0ms
- correction of eyeblink artifiacts through ICA(Independent Component Analysis)
- Exclusion of epochs exceeding +/- 100uV
- Standard and deviant ERP waveform obtained by across-trial averaging and MMN waveform obtained as difference in average waveforms between standard and deviant stimuli
- selection of electrodes giving largest MMN , and average amplitude of selected electrodes was used as MMN of selected participant
- Fishers exact test and Mann-Whitney U-tests comparison of Remission and Non-Remission groups.
- stepwise selecrion method in multiple regression analysis
- measurement of neurocognitive impairment in UHR using Cohens'd test
- correlation between MMN and neurocognitive function

Findings

- MMN reflects functional impairment of NMDA(N-methyl-D-aspartate) receptors(role of NMDA in MMN SZ studies, ketamin, MMN & SZ), it is associated with neurocognitive(current density source in dMMN and SZ, tone duration in SZ/MMN) and functional decline(gray mattter, MMN deficits & functional outcomes).
- amplitude of MMN in response to dMMN predicts remission, improvement in attenuated positive symptoms and functional recovery.(remission prediction using MMN)
- association of MMN to fMMN and global functioning differs from that of MMN to dMMN and global funcioning.()
- baseline dMMN significantly attenuated in UHR group compared to HC and no between group diference in fMMN amplitudes.
- dMMN larger in Remitter group than non-remitter group, and no significatn difference in fMMN in both groups
- neurocognitive functions not significantly reduced in UHR
- reduced dMMN currentsource density in frontal cortex and functional disconnection between frontal and temporal cortices in UHR(46)
- MMN generators found in multiple cortical sources and connectivity among the cortical sources(47,48)
- fMMN and baseline positive symptoms predict ufture neurocognitive function of attention
- consistent fMMN across UHR group subjects
- fMMN may be associated with future but not current neurocognitive function.
- attention neurocognition domain which is associated with fMMN, predicts functioning

EEG and ERP Biomarkers in Individuals at Clinical High Risk for Psychosis

Aim

- Discussion of EEG ERP evidence of abnormalities in CHR-P

Methods

- Quantification of event-related gamma oscillations by transforming time-voltage domain into the time-frequency domain, yielding measures including total power, evoked power and phase-locking factor(PLF) or intertrial phase coherence(108,109)
- Gamma oscillations are often measured using the gamma auditory-steady-state-response(ASSR), an EEG response entrained to click trains(often 500ms or longer) presented at 40Hz driving frequency

State of Knowledge

- P300 & MMN deficits predict conversion to psychosis and/or CHR-P remission but they report only group level differences thus the need of individual predictive accuracy metrics in future studies
- CHR-P criterai can be used to predict future psychosis transition(2), but clinical outcomes vary across CHR-P individuals
  -- algorithms predicting these clinical outcomes have been validated(5,6), they are not accurate enought to predict/support major treatment decisions

Sensory and Perceptual Components

N100

- 100ms negative peak for auditory stimuli in response to infrequent devian auditory stimuli and 150ms for visual stimuli
- reduced among medicate/non-medicated SZ patients and first-degree relatives(7,8,9)
- accompanied by P200, which is distinct topographically and functionally and have both been reported in SZ(10,11)
- associated with severity of symptoms in healthy, CHR-P and psychotic children(16)
- posisble reduction and psychosis conversion prediction of motor induced N2m and its delta frequency oscillatory response (18)
- deficient N100 suppression during self generated speech in SZ patients and first degree relatives(9,20,22)
- deficient N100 suppression during vocalization in CHR-P relative to HCs that correlated with unsual though content severity (22,23)

P50

- elicited during sensory gating paradigm in response to pairs of auditory stimulus seperated by 500ms interstimulus interval at scalp of vertex at approximately 50ms post-stimulus.
- larger at first stimulus(S1) while suppressed at second stimulus(S2) which reflects gating out of irrelevant infromation
- deficiency in gating in terms of ratio of S2 to S1 has been shown in SZ patients(25,27,28,29,30)
- P50 gating deficiency may also be heritable (31,32)

MMN

- dMMN might be more sensitive to SZ than fMMN particularly among first episode patients (42,44,45,46)
- evidence for smaller MMN baseline predicting shorter time to conversion among CHR-P individuals(47,65)
- MMN can distinguish future remitters from non-remitters and predict later functional recovery (66)
- MMN generators have been localized to auditory cortex131 and frontal cortex132,133
- MMN generation has been mapped to the theta frequency band in man136 mand animal131,137 studies
- NMDAR antagonists have been shown to reduce MMN140 and target P300141. thus MMN and P300 deficits in CHR-P converters are consistent with hypothesized NMDAR hypofunction as an underlying pathopsychological mechanism in SZ142,143

Repition Positivity

- a component elicited by standards that increases with successive standard repitiions, consisten with strengthening of the standard's memory trace and associated with the prediction that it will recur (67)
- recent NAPLS show deficient amplitudes in CHR-P individuals both for earliest appearing standards and more prominently for late appearing standards within local sequences of repeating standards following eah deviant (65)
- The deficit was worse in CHR-P individuals who transitioned to psychosis and greater deficits were predictive of shorter time to conversion

P300

- Has two subcomponents: P3b(elicited by infrequent target stimuli subjects must respond to) and P3a(elicited by infrequent non-target novel distractor stimuli requiring no response)
- Both P3b and P3a are reduced in SZ patients and first degree relatives consistent with P300 amplitude reduction reflecting genetic risk for SZ (25,74,75,76,77)

- deficinet P3b amplitudes to auditory(12,15,82-90), to a lesser extent, visual(17,38), target oddball stimuli
- association of target auditory targer P3b with future psychosis onset, differentiating convrters from non-converters reporting medium to large effect sizes (82,83,88,91)
- both auditory(82,83,88) and visual (83) target P3b deficits predict shortertime to psychosis onset
- the NAPLS consortium recently reported that relatively normal auditory target P3b was associated with future CHR-P remission(82)
- P3b predicted improvement in negative and genereal psychopathology symptoms.(93)
- target P300 has been localized to temporo-parietal junction134,135 with amplitude deficinecy potentially implicating compromise of these regions in those at greatest risk.
- P300 has been linked to noradrenergic144, dopaminergic70 and GABAergic systems145 as well as serotonin 5-HT2A146, cholinergic muscarinic147 and cannabinoid receptors148,149

Higher Order Cognitive ERPs

- ERN(Error Related Negativity): response locked ERP elicited by commission errors during choice response(95)
- LPP(Late Positive Potential): reflects emotional reactivity and is greater for both pleasant and unpleasant relative to neutral stimuli(97)
- ERN is reduced in SZ(95)
- SZ patients have generally shpwn intact hedonic response and similar LPP amplitudes to HCs(98, 99)
  A study found attenuated LPP to pleasant and unpleasant stimuli in CHR-P individuals(100)

Neural Oscillations

- Resting state EEG abnormalities in Z patients including increased delta, theta power and reduced alpha power.(101,102)
- identification of EEG spectral abnormalities that predict psychosis conversion including increased delta, theta power alone or in combination with symptom severitry and decresed alpha peak frequency.(103-106)
- SZ is associated woth gamam band abnormalities(30-80Hz), implicated in sensory registration, cross-modal sensory integration and higher order cognitive functions.(107)
- SZ patients have deficit in both power and PLF of the early audiotry gamma response, an obligatory gamma burst evident after 50-100ms following an auditory stimulus. Such deficits have been linked to abnormalities in prevalbumin expressing GABAergic interneurons and NMDARs in SZ.(109-112)

- Gamma ASSR power and PLF deficits are the most replicated gamma oscillation abnormalities in SZ.(113)
- late latency gamma ASSR total power, PLF and gamma evoked power are features that still require investigation and evidence in CHR-P individuals.(63,114,115)
- reduced alpha-ERD to target tones in SZ patients and CHR-P individuals relative to HCs(118-122)
- NAPLS exhxibitted that converter CHR-Ps exhibited reduced alphaERD relative to non-converter CHR-Ps and taht decreased alphaERD predict shorter time to conversion.(122)
- alterations in delta oscillations are associated with P300 deficits observed in SZ(138)