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事件相關電位分析於精神分裂症研究之應用

Application of Event-related Potentials in Schizophrenia Research

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本論文係謝明憲君（學號 d94548003）在國立臺灣大學醫學工程學研究所完成之博士學位論文，於民國 102 年 01 月 05 日承下列考試委員審查通過及口試及格，特此證明

口試委員：

（指導教授）

所長：

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這份論文的完成，首先要感謝醫學工程學研究所電生理暨電子電路實驗室趙福杉教授長久以來的指導與鼓勵，指引我研究的方向。實驗室的學長姐們與學弟妹們，包括乙立、榮隆等人，持續給我不同思路上的啟發。跨出原本臨床醫師已經僵化的思考模式，學習另一種思考領域：這種臨床醫師與工程專業的跨領域合作，是我就讀醫學工程學研究所最大的收穫。

在兼顧臨床工作的沈重負擔下，還能夠讀書與進行研究：得要感激李明濱教授、胡海國教授、高淑芬教授三位歷任部主任的鞭策與提攜。尤其胡海國教授與神經部邱銘章教授，是引領我進入精神分裂症與事件相關電位研究領域的貴人，沒有兩位貴人：我就沒有 2003 年加州大學聖地牙哥分校的一年研究進修，也沒有回台之後的台大醫院精神部神經生理研究室的軟硬體設立與研究助理人力。此外，年輕醫師們在臨床業務與研究上的包容、提醒與溝通，更是催促生性慵懶的我不斷前進的原動力。

感謝家人、特別是內人素玲長期做我臨床工作加上研究所的背後精神支柱。民國 94 年進入醫工所時，雙胞胎旻紘、旻軒同時也國小入學。我一直計畫想跟雙胞胎一起畢業，結果現在雙胞胎已經八年級，比我還壯還高；老三旻哲也都四年級了。謝謝他們。

最後，容我引用美國倫理學家 Michael Josephson 在他的一首”Live a life that matters” 中，提到有意義的人生如下：

“（節錄）……What will matter is not what you bought, but what you built;

not what you got, but what you gave.

What will matter is not your success, but your significance.

What will matter is not what you learned, but what you taught…….”

謹將此論文，獻給我所在乎的人與事。

摘要

精神分裂症是一重大的慢性神經精神疾患。過去的研究結果，均指出此疾患涉及多層面的認知功能缺損，而這些認知功能缺損或可做為標記與界定精神分裂症易感受性基因的內在表現型。然而實際上在對這些認知功能進行量測時的信度常有問題：因為難以判定精神分裂症病患的表現不佳，是否真的不會，還是由於其負性症狀而導致缺乏動機（知道答案，但不想回答）。因此諸如失匹配負波(MMN)、P50/N100這類注意力前(pre-attentional)、不需個案配合測試(task-independent)的事件相關電位，近年來在訊息處理的研究中，已逐漸顯現出其重要性。

P50 與 N100（通常由 Cz 紀錄）；為使用 paired-click paradigm 所進行的聽覺門控(sensory gating)量測；失匹配負波（其中以 Fz 為最顯著）是由聽覺 oddball paradigm 所引發的負向事件相關電位成分波，所對映的是注意力前的聽覺記憶。

在本論文中，進行的四個事件相關電位研究，係依照三個維數層面（疾病狀態層面；事件相關電位與其他量測層面；事件相關電位分析方式層面）來進行

1. 第二章係單獨使用傳統 P50 分析方法。過往的 P50 研究經常強調 S1 的角色(“gating in”)，而本研究則從個案反應中找出 S2 (“gating out”)的重要性。
2. 第三章則進行精神分裂症個案與對照組的失匹配負波與心理衡鑑，合併失匹配負波與心理衡鑑的多元模式，可以有較佳的正確診斷分類。
3. 第四章針對早期廣義的風險狀態(E-BARS)起不同精神病風險程度的受試者，進行事件相關電位分析。我們發現：不論精神病風險程度如何，失匹

配負波所反應出來的偏差檢測受損均已存在；相較之下P50和N100所反應的感覺門控(sensory gating)缺陷則隨著精神病風險程度而有差異。

4. 第五章利用時頻分析：發現相較於控制組個案，精神分裂症個案失匹配負波較差的主要原因，係由於其相位一致性(inter trial phase coherence)不佳。

總之，我們建立了一個包含防電磁隔音艙（硬體）與標準作業流程（人員）的事件相關電位研究室，也建立了與事件相關電位相關的研究相關網路(疾病狀態層面；事件相關電位與其他量測層面；事件相關電位分析方式層面)。事件相關電位是連結基因型（諸如基因與基因表現）跟表現型（諸如人類認知與疾病診斷）之間的橋樑，它能夠增加人類在腦與心智科學上的研究視野。

關鍵詞(keywords):**內在表現型、事件相關電位、失匹配負波、P50、N100、精神分裂症、時頻分析**

Abstract

Schizophrenia is a major chronic neuropsychiatric disorder. Previous studies consistently revealed several cognitive deficits, which may serve as candidate endophenotype markers for identifying the genes for schizophrenia susceptibility. However, the reliability of some cognitive measurements had been criticized since the schizophrenia patients with negative symptoms usually did not have strong motivation to cooperate with such attention-dependent tests. Therefore, the role of pre-attentional, task-independent event-related potentials, such as Mismatch Negativity (MMN) and P50/N100, is important in information processing research.

P50 and N100, usually collected from Cz electrodes, are auditory sensory gating measures using paired-click paradigm. MMN, usually collected from Fz electrodes, is a negative voltage component elicited in an auditory oddball paradigm and represents auditory sensory memory.

In this dissertation, we proposed 4 different views of ERP research according to the three dimensions (Disorder dimension; ERP and other measure dimension; ERP analysis method dimension) :

1. Chapter 2 demonstrated a traditional P50 analysis method alone. Previous studies have placed more emphasis on S1's role in P50 sensory (“gating in”) while our study highlights the significant role played by the S2 response (“gating out”).
2. In Chapter 3, MMN was combined with several neuropsychological measurements to differentiate schizophrenia patients from healthy subjects. The multivariate approach combining MMN and neurocognition had a better classification utility.

3. Chapter 4 calculated the ERP in high-risk group (suspected pre-psychotic state, also called E-BARS, early/broad at-risk mental states) vs. control subjects. Impaired deviance detection shown by MMNs already exists in people at a pre-psychotic state regardless of clinical severity, while sensory gating deficits shown by P50/N100 varies depending on the risk levels in prodromal period.
4. Chapter 5 utilized time-frequency analysis for MMN and we found subjects with schizophrenia have lower inter trial phase coherence than controls.

In conclusion, we built up an ERP laboratory with sound-attenuating and electrically shielded booth, standard operation procedure for ERP. We also set up ERP research network in three different dimensions. ERP is a bridge connecting genotype (gene, gene expression) and phenotype (human cognition and disorder). ERP actually made a lot of impact in brain and mind research.

關鍵詞(keywords) **: Endophenotype, Event related potential, Mismatch negativity, P50, N100, Schizophrenia, Time-frequency analysis**

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Chapter 1. Introduction

1.1 Schizophrenia as Important Human Health Challenges

Schizophrenia is a major and chronic neuropsychiatric disorder. According to WHO, it is one of the leading causes of YLD (years lost due to disability), regardless of sex and income (WHO, 2004). It is a devastating disease which has a wax and wane course, leading to direct and indirect costs of $100Billion/ year in USA (Kane, 1996) or 1.85 Billion/year in Australia (2005).

Schizophrenia is a multifaceted disturbance (Please refer to Figure 1.1). Predisposing genetic factors interact with environmental factors, and their interactions trigger a complex cascade of pathophysiological processes in the developing brain. The first changes most likely include gene expression alterations and a variety of neurochemical-metabolic disturbances. The altered brain homeostasis affects the normal wiring of the brain, resulting in inefficient information processing in the affected individuals. The combined changes ultimately lead to behavioral, cognitive and emotional deficits, which are the clinical hallmarks of the disease (Horvath & Mirnics, 2009). The final result (schizophrenia) represents a pervasive deficit in brain function, and neuroscience tools also provide us more brain insights and have been one of the focus of schizophrenia research in recent years(Blow, 2008; Javitt et al., 2008; Keshavan et al., 2008).

In order to explore the complex pathophysiological pathways of schizophrenia from genotype to phenotype (Keshavan et al., 2008), several of the observed neurobiological alterations, which are apparently derived from different domains, are likely to be inter-correlated and may be related to each other (Please refer to Figure 1.2). Several endophenotypes may represent consecutive “nodes” on common pathophysiological

pathways from the genotype to the phenotype. Current research has turned to the endophenotype strategy to reveal susceptibility genes (Price et al., 2006; Bender et al., 2007; Turetsky et al., 2007; Johannesen et al., 2012).

1.2 Event-related Potential (ERP)

ERP, event related potential, is one of the most widely used methods in cognitive neuroscience research to study the physiological correlates of sensory, perceptual and cognitive activity associated with processing information(Handy, 2005). It constitute a millisecond-by-millisecond record of information processing, while the temporal resolution is vastly greater than other functional neuroimaging techniques such as functional magnetic resonance imaging (fMRI) or Positron Emission Tomography (PET) (Hillyard & Kutas, 2002; Kuperberg, 2004; Niznikiewicz et al., 2004). Besides, it is non-invasive (in respect of SPECT/ PET) and associated with relatively low cost for setup and maintenance (in respect of MEG/ fMRI/ PET). Auditory event-related potentials (ERP), including P50, N100, and mismatch negativity (MMN), have been utilized to study normal versus defective information processing in schizophrenia(Adler et al., 1982; Nagamoto et al., 1991; Clementz et al., 1997; Michie, 2001; Keshavan et al., 2008)

Although some neurocognitive measure had been assessed in schizophrenia patients, the reliability of some cognitive measurements in schizophrenia research had been criticized because the schizophrenia patients with negative symptoms (blunted affect, anhedonia, avolition, associality and attention deficit) usually did not have strong motivation to cooperate with such attention-dependent tests such as neuropsychological tests, P300, etc (Kane, 1996; Goldberg et al., 2003). In contrast, some pre-attentional, automatic cognitive processes that are not influenced by subjects' motivation, including

P50, N100 and MMN, are the current research focus of information processing in schizophrenia patients (Braff & Light, 2004).

1.3 P50 and N100

Sensory gating to irrelevant sensory input is a safeguard filtering mechanism of the central nervous system. It helps to prevent incoming irrelevant/redundant sensory information from entering into the higher cortex and to ensure normal information processing (Braff & Geyer, 1990). Successful sensory gating is an important property of the normal functioning brain. Deficits in sensory gating can result in an overflowing of irrelevant stimuli into the higher cortex, which may lead to brain dysfunction, including schizophrenia (Light & Braff, 2003).

There are two aspects to sensory gating: (1) the capacity to cease to respond or to significantly reduce the magnitude of an individual response to incoming irrelevant stimuli (“gating out”); and (2) the capacity to re-respond when a novel stimulus is presented or a change occurs in ongoing stimuli (“gating in”)(Boutros et al., 1991). Sensory gating activity may be as early as the P50 (40 to 75 msec) and as late as the N100 (Boutros et al., 1991; Smith et al., 1994).

Sensory gating methods, including P50 and N100, using paired-click paradigm and measured from Cz electrodes (Nagamoto et al., 1989; Nagamoto et al., 1991) had provided strong relationship between genes and the pathophysiological aspect of schizophrenia (i.e. the chromosome l5ql4 locus of the alpha-7-nicotinic receptor gene was associated with the P50 sensory gating abnormalities) (Freedman et al., 1997). They have also been identified as candidate endophenotypes of schizophrenia in order to reveal possible schizophrenia genes (Turetsky et al., 2007; Turetsky et al., 2008; Rissling &

Light, 2010a).

Although both P50 and N100 are sensory gating measures, they are independent phenomena. P50 is not intrinsically auditory phenomena, and appears to involve frontal cortical activity. In contrast, N100 suppression is most likely based on refractory mechanisms intrinsic to the auditory system (Kisley et al., 2004; Hanlon et al., 2005; Oranje et al., 2006). N100 deficit specific to schizophrenia may be due to deficits in the primary auditory cortex or NMDA neurotransmitter system (Javitt, Jayachandra, et al., 2000).

1.4 Mismatch Negativity

The mismatch negativity , MMN, is a negative deflection of the auditory event related potential (ERP) when recorded at frontal electrodes(Fz, FCz) which is elicited task-independently by an unpredictable/infrequent change in a in a train of standard repetitive sounds(Naatanen et al., 1978). It is evoked by an infrequently presented stimulus ("deviant"), differing from the frequently-occurring stimuli ("standards") in one or several physical parameters like duration, intensity, or frequency(Näätänen, 2003). Successful processing of sensory inputs requires the ability to facilitate responses to less frequent salient stimuli, while MMN indicates the measures of impaired deviance detection (Turetsky et al., 2007). It has been proposed that this pre-attentional mismatch detection process plays an important role in initiating involuntary switching of attention toward an auditory stimulus change outside (before) the focus of attention (Naatanen & Michie, 1979; Giard et al., 1990).

MMN is smaller in schizophrenic patients than in comparison groups (Shelley et al., 1991; Light & Braff, 2005a, 2005b), and is probably an index of auditory echoic memory (auditory sensory memory) and a part of the pre-attentional auditory

information processing (Näätänen et al., 1989; Catts et al., 1995; Javitt et al., 1995; Naatanen & Winkler, 1999; Michie et al., 2000; Niznikiewicz et al., 2004; Cooper et al., 2006). Mismatch negativity (MMN) may be a surrogate index of NMDA receptor function (Javitt et al., 1996; Keshavan et al., 2008). Besides, deficits in MMN persisted following treatment with antipsychotics (Umbricht et al., 1998, 1999; Korostenskaja et al., 2005).

The heritability of MMN is high (~68%), suggesting a significant genetic contribution (Ahveninen et al., 2006; Hall, Schulze, Bramon, et al., 2006; Hall, Schulze, Rijsdijk, et al., 2006). The MMN deficit has been shown to be a robust candidate endophenotype for schizophrenia (Turetsky et al., 2007; Keshavan et al., 2008).

1.5 Overall Aims of this Dissertation

According to the literature review above, ERP serves as an essential bridge between phenotype and genotype (Figure 1.1 and 1.2) in order to explore pre-attentional, automatic information processing. In fact, according to Turetsky et al., successful processing of sensory inputs requires two kinds of ability (Braff & Light, 2005; Turetsky et al., 2007):

1. the ability to inhibit intrinsic responses to redundant stimuli
2. the ability to facilitate responses to less frequent salient stimuli

Both of these pre-attentional processes are "impaired" in schizophrenia.

1. P50/N100 suppression represents the measures of inhibitory failure (i.e. inability to filter out redundant stimuli, or a failure of ‘sensory gating’)
2. MMN indicates the measures of impaired deviance detection

The aims of my doctoral dissertation include establishing an ERP laboratory and utilizing ERP in a coordinated research network which comprises three different dimensions (Figure 1.3: Disorder Dimension; ERP and other measure Dimension; ERP analysis method Dimension):

1. Chapter 2 demonstrated a traditional ERP(P50) analysis method alone in schizophrenia patients vs. control subjects.
2. Chapter 3 analyzed the results between MMN and neurocognition in schizophrenia patients vs. control subjects.
3. Chapter 4 compared the ERP(P50/N100/MMN) in high-risk group(suspected pre-psychotic state) vs. control subjects.
4. Chapter 5 utilized time-frequency analysis for MMN in schizophrenia patients vs. control subjects.
5. Chapter 6 summarized current achievements and future work.

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1.6 Tables and Figures

Figure 1.1 Schizophrenia: from gene, environment to clinical aspects. ERP represents an effective measure of altered information processing (modified from Horvath & Mirnics, 2009)

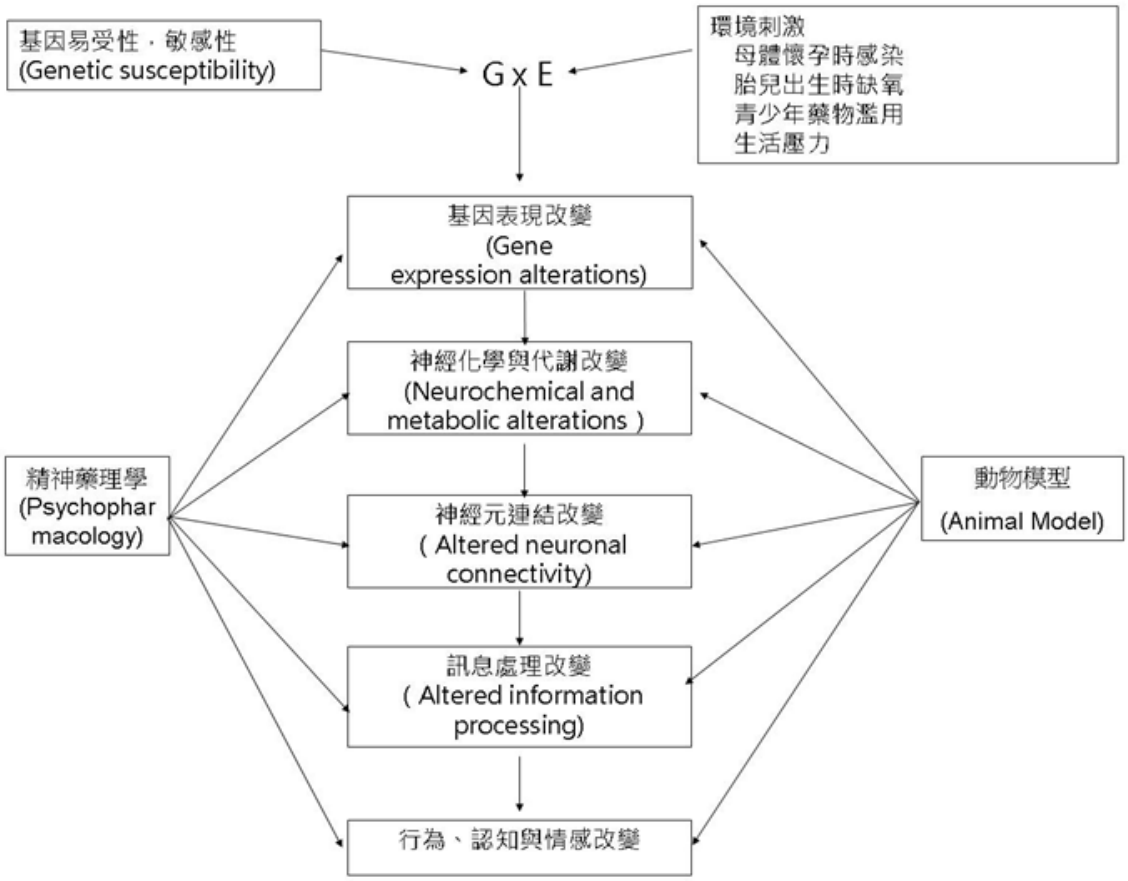


Figure 1.2 Pathophysiological pathways from the genotype to the phenotype. Intermediate phenotypes (i.e. endophyotype)may serve as nodes in this causal chain. (Source: Keshavan et al., 2008)

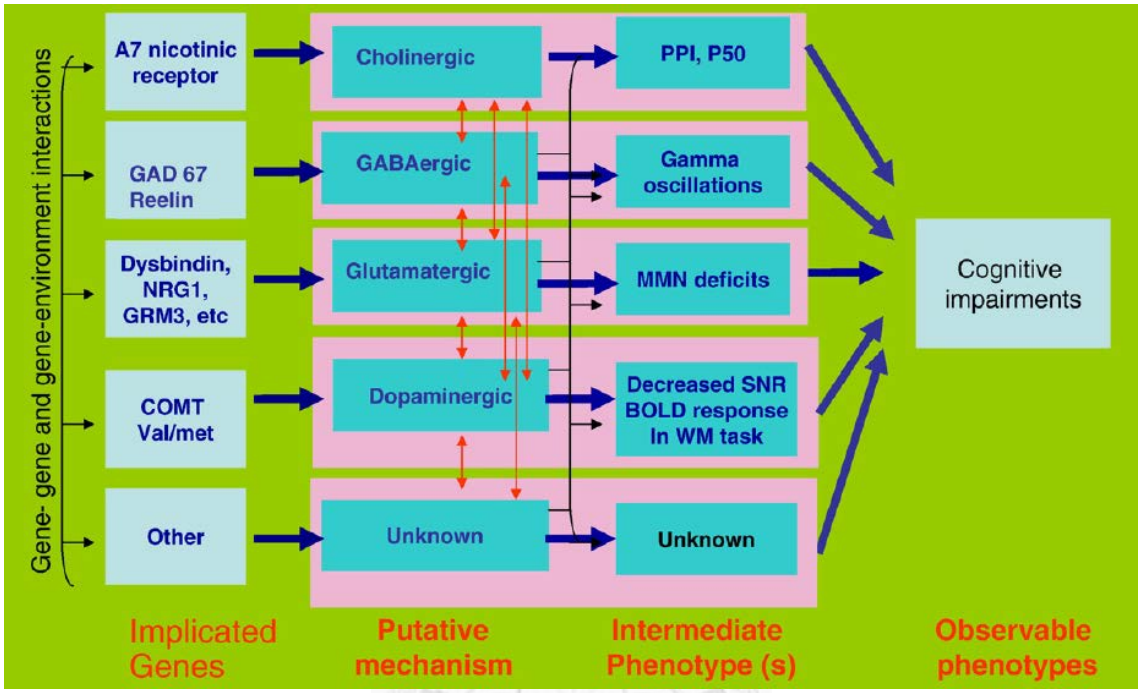
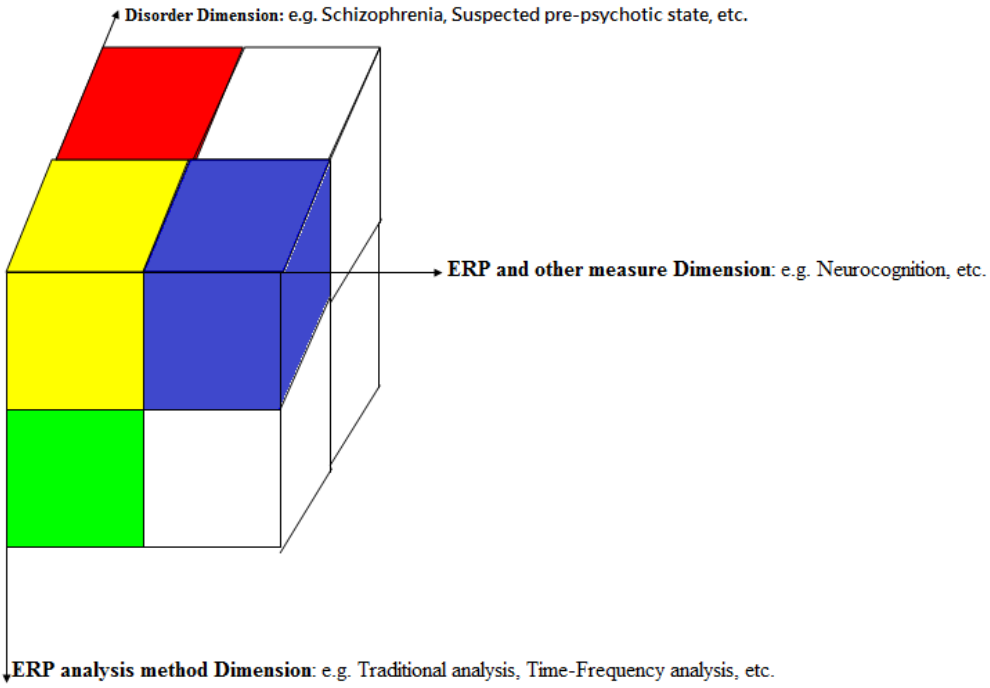


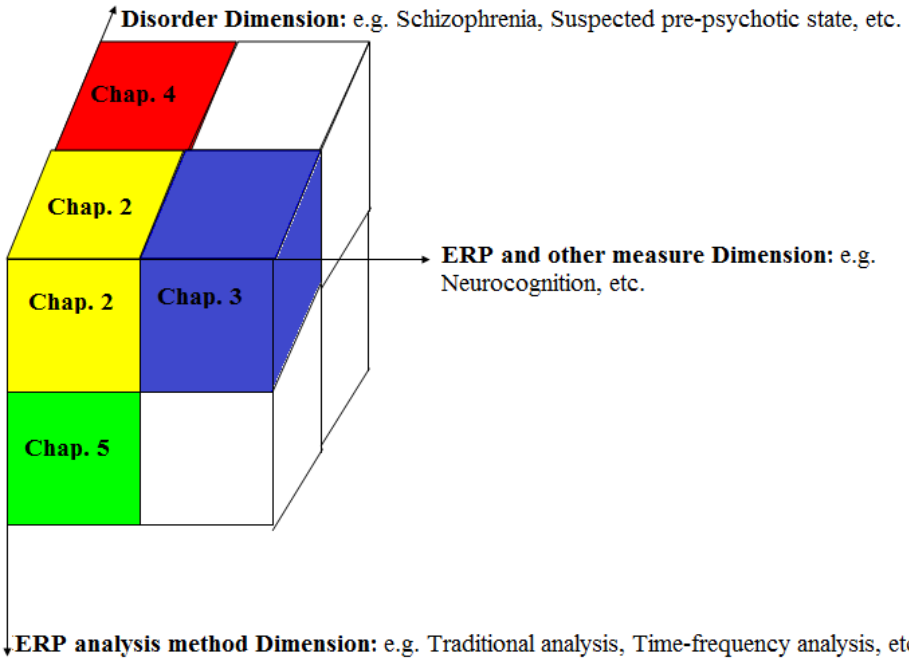
Figure 1.3 Dimensions of ERP research.

(A) Three dimensions of ERP application, (B) Context of this dissertation.

(A)



(B)



Chapter 2. More Evidence to Support the Role of S2 in P50 Studies

2.1 Background

With great interest, we read the inspiring article by Hong et al.(2009). In this excellent study, the researchers made an effort to investigate the longitudinal relationship between P50 sensory gating, symptomatology, and different antipsychotics in first-episode never-medicated schizophrenia patients, providing an opportunity to increase our under-standing of P50 gating. We noticed one of their findings–the important role of an increased S2 amplitude (instead of a reduced S1 amplitude) in P50 sensory gating deficits–was inconsistent with the majority of findings in the literature (Nagamoto et al., 1989; Myles-Worsley et al., 2004; Swerdlow et al., 2006).

A discussion of some experimental procedures is worth-while. First, Hong et al. did not mention whether they used the 0.5 μV criterion to recognize the S1 amplitude. Due to the small signal-to-noise ratio of P50 potentials, especially in schizophrenia patients, only epochs beyond 0.5 μV should be qualified for actual P50 waves (Yee et al., 1998; Turetsky et al., 2007; Boutros, 2008). Second, Hong et al. only analyzed 32 pairs of auditory clicks. Despite no consensus on the appropriate number of trials, most P50studies carried out more than 60 trials (de Wilde et al., 2007); the more trials included in the average P50 response, the better the signal-to-noise ratio (de Wilde et al., 2008). Finally, participants in Hong's study were seated upright, possibly risking aggravating muscle artifacts(de Wilde et al., 2007).

2.2 Methods

From April 2006 to April 2008, 81 DSM-IV schizophrenia patients and 47 healthy controls were recruited, none of whom had a history of seizure, head trauma, or hearing impairment. Each participant signed IRB-approved written informed consent. All participants, free-of-smoking for at least 1 h before sessions(Adler et al., 1992; Olincy & Martin, 2005), were asked to lie down to be studied in the supine position. Electrodes at the nose tip and the Fpz served as the reference and ground, respectively. An auditory conditioning-testing paradigm, paired-clicks (1 ms, 85 db) presented every 8–12s throughout the whole session(average: 10 ms) with a 500-ms inter-stimulus interval, was used (Clementz et al., 1998; de Wilde et al., 2007) until 120 artifact-free trials were collected online. Programmed automating procedures using TCL batch processing language, begun with EOG artifact reduction, were used for offline data processing. A 1–50 Hz band pass filter was then applied and P50 was measured from the Cz. P50 event-related potentials were identified based on Nagamoto et al.'s (1989) criteria. P50 parameters included the S1 amplitude, the S2 amplitude, the difference between the S1 and S2amplitude, and the P50 gating ratio (S2 amplitude/S1amplitude).

2.3 Results

The means of the S2 amplitude and the P50 gating ratio of the patient group were significantly larger than those of the controls, but the means of the S1 amplitude and the amplitude difference were not. In the patient group, both the S1 amplitude and S2 amplitude significantly correlated to the P50 gating ratio (S1: r=−.264, p=0.017; S2: r=.6367, p<0.001). Notably, the P50 gating ratio only correlated to the S2 amplitude in the control group (S1: r=−.057, p=0.702; S2: r=.819, pb0.001). In summary, by applying

0.5 μV criteria and more trials recommended by the experts, our study showed the high S2 amplitude in schizophrenia patients, not the S1 amplitude, played a more important role in their deviant P50 sensory gating when compared to healthy participants. Although our patients were not first-episode never-medicated, our results were compatible with Hong's findings. In fact, another recent study recruiting normal participants, new-onset and chronic patients also supported this viewpoint (Fresan et al., 2007).

2.4 Discussion

This study complements Hong's study (Table 2.1). However, a contradictory conclusion–a reduced S1amplitude contributed more than an increased S2 amplitude to an increase in the P50 gating ratio among schizophrenia patients–was reached in many previous preclinical and clinical studies (for example Myles-Worsley, 2002; Nagamoto et al., 1989; Swerdlow et al., 2006). Indeed, this inconsistency reflects the need for further understanding of the mechanism of P50 sensory gating and the meaning of individual P50 parameters. Some have suggested theS1 response represents information registration (“gating in”) and the S2 responsereflects habituation of repeated auditory stimuli (“gating out”) (Brockhaus-Dumke et al., 2008). For our patient group, the S1 amplitude correlated significantly to the P50 gating ratio despite the lack of differences with the control group. This might be evidence supporting an assumption that the inhibitory mechanism begins at the S1 response and manifests at the S2 response(Fresan et al., 2007). Concerning whether applying the 0.5 μV criterion affects finding a reduced S1 response in schizophrenia patients, Nagamoto who first proposed the 0.5 μV criterion, in fact, depicted schizophrenia patients as having diminished S1 amplitudes simultaneously (Nagamoto et al., 1989). In conclusion, previous studies have placed more emphasis on S1's role in P50 sensory “gating in” and its clinical correlation

(Myles-Worsley, 2002; Potter et al., 2006; Swerdlow et al., 2006). However, the result of the study of Hong et al., as well as that of our current study, highlights the significant role played by the S2 response (“gating out”). Therefore, more detailed descriptions of associated methodological issues are encouraged to replicate and validate related research across different laboratories before a consensus on the experimental paradigm is established. There is room for further understanding of P50 sensory gating and its underlying mechanism before it can be a candidate endophenotype of schizophrenia.

Table 2.1 Comparison of clinical characteristics and P50 parameters between healthy participants and schizophrenia patients.

	Schizophrenia ($N=81$)	Controls ($N=47$)	p-value (chi^2)
Male/female	42/39	19/28	0.212 [a]
Smoker/non-smoker	16/65	3/44	0.043 [b]
Medication			
FGA	12	–	N/A
SGA	56	–	N/A
FGA + SGA	11	–	N/A
2 SGAs	2	–	N/A
	Mean ± S.D.	Mean ± S.D.	p-value (t-test)
Age (years)	37.78 ± 10.70	28.39 ± 7.61	<0.001
Age at Onset (years)	23.01 ± 7.51	–	N/A
Duration (years)	14.77 ± 9.81	–	N/A
PANSS subscales			
Positive	12.07 ± 4.45	–	N/A
Negative	15.10 ± 5.92	–	N/A
General	25.23 ± 7.72	–	N/A
P50 parameters			
Trials	107.70 ± 24.1	117.80 ± 20.9	0.018
S1 latency (ms)	61.48 ± 8.19	62.04 ± 7.08	0.696
S1 amplitude (μV)	2.37 ± 1.24	2.21 ± 0.81	0.439
S2 amplitude (μV)	1.02 ± 0.81	0.72 ± 0.64	0.028
S1–S2 amplitude (μV)	1.35 ± 1.14	1.50 ± 0.81	0.395
Gating ratio	0.49 ± 0.44	0.33 ± 0.30	0.030

FGA = first-generation antipsychotics; SGA = second-generation antipsychotics.

[a] Pearson's chi-square test.

[b] Fisher's exact test.

Chapter 3. Differentiation of Schizophrenia Patients from Healthy Subjects by Mismatch Negativity and Neuropsychological Tests

3.1 Introduction

Schizophrenia is recognized as a neurobiological syndrome with heterogeneous presentation and pathophysiology. The development of biological markers is important in schizophrenia research, which is restricted by the phenomenology-based diagnostic system. Biological markers are measurable traits that are specific to particular conditions and have diagnostic and predictive values. Several measurements have been reported to discriminate schizophrenia patients from healthy controls, such as quantitative electroencephalography and event-related potentials (ERP)(Gerez & Tello, 1995). However, a single marker may not be able to address the heterogeneous nature of schizophrenia.

Mismatch negativity (MMN) is a negative component of auditory event-related potentials elicited when infrequent discernible deviant sounds (“oddballs”) occur in a sequence of repetitive standard sounds. The MMN response relies on the established memory trace of standard sounds and is an index of automatic pre-attentional sensory processing of auditory input and echoic memory (Naatanen et al., 1978; Winkler et al., 1996; Naatanen & Winkler, 1999; Baldeweg et al., 2004; Naatanen et al., 2007). MMN deficit has been shown to be a robust feature for chronic schizophrenia patients(Umbricht & Krljes, 2005) and is regarded as a candidate endophenotype for schizophrenia (Turetsky et al., 2007; Keshavan et al., 2008). Some studies suggested that MMN deficit is specific to schizophrenia (Towey et al., 1994; Catts et al., 1995; Oades et al., 1996;

Oades et al., 1997; Umbricht et al., 2003) and is unrelated to neuroleptics treatment (Schall et al., 1998; Umbricht et al., 1998, 1999; Shinozaki et al., 2002; Korostenskaja et al., 2005). However, MMN deficit has ever been observed for subjects with bipolar disorder (Andersson et al., 2008; Takei et al., 2010) or Asperger syndrome (Jansson-Verkasalo et al., 2003; Lepisto et al., 2006; Lepisto et al., 2007). Furthermore, MMN alone may not be adequate to predict whether an individual subject has schizophrenia or not. The effect size of MMN deficit for schizophrenia is around 0.99, and it implies that the distributions of MMN of controls and schizophrenia patients overlap(Umbricht & Krljes, 2005). In the literature, only one study has applied MMN in the context of multivariate electrophysiological endophenotype approach (MMN, P50, P300, and antisaccades) to predict the diagnostic groups (Price et al., 2006). The study found that a weighted combination of the four markers could provide better power in prediction. In addition to the multivariate approach, using markers measured by different modalities may improve the predictive power further (Pardo et al., 2006). To date, there have been no study on MMN in Han Chinese schizophrenia patients. The current study thus aims to evaluate the performance of combining MMN with neuropsychological tests to differentiate schizophrenia patients from healthy subjects in a population of Han Chinese Ethnicity.

The pattern of discriminating schizophrenia patients from healthy subjects by MMN is related to the types of deviant stimuli and aging. Todd et al. showed that patients at the early course of schizophrenia had deficits in duration and intensity MMN, but not frequency MMN. With longer length of illness, the frequency MMN deficit became significant (Todd et al., 2008). Frequency MMN deficits were not found in first-episode schizophrenia patients (Salisbury et al., 2002; Umbricht et al., 2006; Magno et al., 2008)

or patients with recent-onset schizophrenia (Javitt, Shelley, et al., 2000). One study found significant reduction in chronic schizophrenia patients and marginal reduction in recent-onset schizophrenia patients for both duration and frequency MMN (Javitt, Shelley, et al., 2000). Marginally decreased duration MMN amplitudes, rather than frequency MMN was noted for subjects exhibiting prodromal symptoms of schizophrenia (Brockhaus-Dumke et al., 2005). These studies suggested MMN deficits are related to the progression of schizophrenia, and duration MMN might be a more sensitive marker in the early stage of the disease. However, two studies were unable to find duration MMN deficits in first-episode schizophrenia patients (Umbricht et al., 2006; Magno et al., 2008). In addition, the age-related declination of MMN observed in healthy subjects further complicated the interpretation of progressive MMN reduction with the course of schizophrenia (Czigler et al., 1992; Woods, 1992; Pekkonen, 2000; Kisley et al., 2005; Cooper et al., 2006; Ruzzoli et al., 2012). Salisbury et al. conducted a follow-up study for a group of first-hospitalized schizophrenia patients. Frequency MMN amplitude of schizophrenia patients was not different from age-matched controls initially, but 1.5 years later patients showed significant MMN reduction which was correlated with the reduction of left Heschl's gyrus gray matter (Salisbury et al., 2007). The study by Todd et al. found significant age-related decline of duration MMN for both healthy subjects and schizophrenia, but the age-related decline of frequency MMN was only observed in schizophrenia patients (Todd et al., 2008). Similarly, Kiang et al. also found age-related decline of duration MMN for both controls and schizophrenia patients (Kiang et al., 2009). In summary, with the course of schizophrenia, the duration MMN deficit remains stable and its gradual reduction seems to be related to aging. To the contrary, frequency MMN is related more to the progression of pathology of schizophrenia. Therefore, we chose to look at duration MMN for the prediction of diagnostic groups.

Cognitive impairment is a core feature of schizophrenia, with high intra-group heterogeneity (Palmer et al., 2009). The effect size of a single neuropsychological test to differentiate patients from healthy controls has been reported to be around 0.46 to 1.57, with the largest effects in global verbal memory and processing speed measured by digit symbol coding(Heinrichs & Zakzanis, 1998; Dickinson et al., 2007). But the distribution of test scores of schizophrenia patients overlapped with that of healthy subjects, and no single test was able to satisfactorily separate the two groups. The Continuous Performance Test (CPT) and Wisconsin Card Sorting Test (WCST) are two neuropsychological tests widely applied in the research of schizophrenia. The CPT is an index of sustained attention, early visual information processing, and response inhibition. During the CPT session, numbers from 0 to 9 are randomly presented to the subjects. They need to respond whenever the number “9” appears following the number “1”. The WCST is used as a complex measurement of executive function, where mental flexibility, working memory, and goal-directed behaviors are involved. The WCST requires subjects to match a series of 128 response cards one by one to the stimulus cards according to color, form, or number. After each trial, “right” or “wrong” is fed-back without telling the correct sorting principle. Subjects have to figure out the right principle and correctly complete 10 consecutive trials. Then the sorting rule changes, and subjects need to find the new rule. Schizophrenia patients have poorer performance on both the CPT and WCST, with reported effect sizes of 0.66 to 1.13 and 0.81 to 1.00 respectively (Dickinson et al., 2007).

In this study, we applied a multivariate approach to classify schizophrenia patients and healthy subjects using MMN and several neuropsychological markers (CPT, WCST, and the intelligence test). We first explored the MMN deficit and potential covariates. On developing the predictive model, the correlation between the two groups of markers were

analyzed. Then in logistic regression modeling, useful predictive markers were selected and combined to construct a probability model to predict diagnostic grouping.

3.2 Materials and Methods

3.2.1 Subjects

One hundred and twenty stable outpatients, aged 18 to 65 years who met the DSM-IV criteria for schizophrenia, and 76 age- and gender-matched healthy controls were recruited. The study was approved by the Institutional Review Board of the National Taiwan University Hospital. Written informed consent was received from all participants. Each schizophrenia patient's capacity to consent was evaluated by his/her treating psychiatrist who made the referral to this study. When the capacity to consent was reduced, consent from another family member was required in addition to the patient's own consent. All subjects were interviewed using the Chinese version of the Diagnostic Interview for Genetic Studies (DIGS) (Chen, Liu, et al., 1998). Then two board-certified psychiatrists independently made the diagnoses according to the DSM-IV-TR criteria by reviewing the DIGS data and medical charts. If the diagnoses were inconsistent, a senior psychiatrist would made the final diagnoses. Subjects with mental retardation, schizoaffective disorders, bipolar affective disorder, organic mental disorders, and substance-related disorders were excluded. The controls had no lifetime or current psychiatric diagnosis or family history of psychotic disorders. Subjects were excluded if they had epileptic disorders or other major brain pathology. The age of onset and Positive And Negative Syndrome Scale (PANSS) scores were recorded for the patients (Andreasen, 1990). In addition, daily doses of antipsychotic agents were transformed into chlorpromazine equivalents by the formulas using regression with power transformation by Andreasen (Andreasen et al., 2010).

3.2.2 Electroencephalographic procedure

The standard protocol for MMN for the experimental paradigm and data processing reported by Light et al. was followed (Light et al., 2010). Audiometry testing was used to exclude subjects who could not detect 40-dB sound pressure level tones at 500, 1000, and 6000 Hz presented to either ear. Subjects were seated in a comfortable recliner in a sound-attenuating and electrically shielded booth. They were instructed to relax and to watch a silent benign cartoon film presented on a 19-inch LCD monitor screen located at eye level to reduce eye movements over the session. During the test session, subjects were closely observed through a video monitor and EEG for signs of sleep or slow wave activity. When encountered, the experimenter spoke briefly to wake up the subject.

The auditory stimuli were generated by a Neuroscan STIM system and were presented to subjects binaurally via foam insert earphones. The data was recorded by a Neuroscan ACQUIRE system (NeuroScan, Inc., El Paso, TX). The EEG signals were recorded with an electrode cap (Quik-Cap, NeuroScan, Inc., Charlotte, NC) from 32 scalp locations (10-20 system). Electrodes placed at the tip of the nose and at Fpz served as the reference and ground, respectively. Four additional electrodes were located above and below the left eye and at the outer canthi of both eyes to monitor blinks and eye movements. Electrode impedances were kept below 5 kΩ prior to MMN recording.

An auditory oddball paradigm of duration MMN of approximately 30-min duration was given. The cartoon soundtrack was turned off and replaced by the experimental 85-dB auditory stimuli, which were presented at a fixed 500 msec onset-to-onset asynchrony. The duration of standard stimulation and deviant stimulation were 50 msec and 100 msec, respectively. Stimuli occurred in a pseudorandom order with probability of

occurrence 0.9 for standard tones and 0.1 for deviant tones. Stimuli signals were digitized at a rate of 1 kHz and an on-line band-pass filter at 0.5-100 Hz, without 60-Hz notch filter. During testing, online ERP averages to standard and deviant tones were also acquired to monitor signal quality and the number of sweeps free of gross artifacts (defined as ±100 μV across the -100~500 msec following stimuli). The MMN session was continued until a minimum of 225 artifact-free deviant trials had been collected on-line.

3.2.3 EEG data processing

All data were processed using Neuroscan Edit 4.3 software (Compumedics USA, Charlotte, North Carolina). Semi-automated procedures using the Tool Command Language (TCL) batch processing language began with EOG artifact reduction through a built-in pattern-recognition algorithm (Semlitsch et al., 1986). The subject's continuous data files were then epoched 100 msec pre-stimulus to 500 msec post-stimulus. Following linear detrending and baseline correction to the average pre-stimulus interval, all epochs containing amplitudes exceeding ±50 μV in frontal recording sites (F7, F8, Fp1, Fp2, F3, F4, and Fz) were automatically rejected. EEG responses to standard and deviant stimuli were separately averaged to create a standard ERP and a deviant ERP, and both were low-pass filtered at 20 Hz (0-phase shift and 24-dB/octave roll-off) to remove any residual high-frequency artifacts. MMN waveforms were generated by subtracting the standard ERP from the deviant ERP. MMN indices were measured as the mean voltage from 135 to 205 milliseconds (Michie et al., 2002; Light & Braff, 2005b, 2005a; Wynn et al., 2010).

3.2.4 Neuropsychological tests

All subjects received MMN examinations, and most of them received the neuropsychological test batteries, including the Continuous Performance Test (CPT) for 114 patients and 70 healthy subjects, Wisconsin Card Sorting Test (WCST) for 115 patients and 71 healthy subjects, and Wechsler Adult Intelligence Scale Third Edition (WAIS-III) for 102 patients and 72 healthy subjects (Weschler et al., 2002). The detailed procedures of the CPT and WCST have been described in previous publications. In brief, subjects completed two 5-minute CPT sessions: the undegraded 1-9 task, and the 25% degraded 1-9 task (Chen, Hsiao, et al., 1998). Sensitivity indices indicating the ability to discriminate target from non-target trials were calculated (d' for undegraded CPT and md' for degraded CPT). The WCST results were scored as four indices defined in the WCST manual as: (1) perseverative errors: number of errors that were perseverative reflecting the tendency towards perseveration; (2) categories achieved: the number of times 10 consecutive correct responses were made, reflecting overall success; (3) trials to complete first category: number of trials needed to complete the first category; and (4) conceptual level response: proportion of consecutive correct responses occurring in runs of 3 or more, reflecting insight to the correct sorting principles (Heaton et al., 1993). Index scores of CPT and WCST were transformed to adjusted z score by adjustment for age, sex and education level based on the data of the healthy subjects (Chen, Hsiao, et al., 1998; S. H. Lin et al., 2011). The Chinese version of WAIS-III was applied (Weschler et al., 2002). In addition to Verbal IQ, Performance IQ, and Full Scale IQ scores, several scaled scores of subtests and one composite secondary index were also used, including (1) Information: a measure of acquired general knowledge; (2) Arithmetic: a mental arithmetic task that measures working memory; (3) Digit Span: measuring working memory free from distraction; (4) Block Design: reflection of visuospatial and motor

skills; (5) Digit Symbol-coding: assessment of processing speed; (6) Working Memory Index: a composite index composed of Arithmetic and Digit Span.

3.2.5 Statistical analysis

Statistical analysis was conducted with the SAS software package, version 9.2 (SAS Institute Inc., Cary, NC, USA). A two-sided p-value less than or equal to 0.05 was regarded to be statistically significant. Continuous data and categorical data were presented with mean ± standard deviation (SD) and frequency (percentage), respectively. The Student's t-test and chi-square test were used to compare data between groups. A mixed-model repeated-measures ANOVA was applied for two analyses on the comparison of MMN between patients and controls. The first analysis examined MMN amplitudes recorded from all electrodes over the scalp, with the 32 electrodes as the within-subject factor. The second analysis was focused on midline electrodes, with electrode site (Fz, FCz, Cz, CPz, Pz, and Oz) as the within-subject factor. Group was the only between-subject factor, and age was the only covariate. Huynh-Feldt corrections were applied when the degree of freedom was more than 1. The correlation between MMN at electrode Fz and the neuropsychological tests were explored by Pearson's partial correlation, controlling for covariates significantly associated with MMN.

To identify the predictive factors for schizophrenia, multivariate logistic regression models were applied to find parsimonious regression models that fit the observed data. The MMN value at each electrode and all neuropsychological indices listed were included as potential predictive variables. Then stepwise variable selection procedure was used, where the significance levels for entry and for stay were set to 0.15 initially, and then reduced to 0.05 to identify the best final model. Both the goodness of fit (GOF) measures (the percentage of concordant pairs and adjusted generalized R2) and the GOF

tests (deviance GOF test, Pearson chi-squared GOF test, and Hosmer-Lemeshow GOF test) were used to assess the GOF for the fitted model. The percentage of concordant pairs indicated the proportion of "concordant" pairs where case (i.e., the observed binary response is 1) had the highest predicted event probability among all possible case-control pairs. A larger percentage of concordant pairs suggested a better fit of the logistic model. Larger p values were preferred for the three GOF tests when the null hypothesis was that the logistic regression model fit the observed binary data well. Finally, statistical tools for regression diagnostics such as residual analysis, detection of influential cases, and check for multi-collinearity were applied (Hosmer & Lemeshow, 2000; Rosner, 2006).

3.3 Results

3.3.1 Subjects

Comparisons of demographics and neuropsychological tests between the schizophrenia patients and healthy subjects are shown in Table 3.1. The mean Positive And Negative Syndrome Scale (PANSS) score of the patients was 53.0±15.1. Twenty percent of them received first generation antipsychotics, 62.5% received second generation antipsychotics, and the remaining 17.5% received clozapine. The mean chlorpromazine equivalent dose was 379.8±243.9 mg/day.

3.3.2 Mismatch negativity

Grand average MMN waveforms for each group are shown in Figure 3.1. Repeated-measures ANOVA showed a significant main effect of group ($F(1,182) = 6.57$, $p = 0.0112$) and electrode x group interaction ($F(31,5642) = 11.78$, $p < 0.0001$, Huynh-Feldt $\varepsilon = 0.1268$) on MMN across electrodes. Age was a significant covariate (age main effect: $F(1,182) = 10.41$, $p = 0.0015$; age x electrode: $F(31,5642) = 13.85$, $p <$

0.0001, ε = 0.1268) and was thus included in following analyses. In both schizophrenia and control groups, amplitudes of MMN reduced with increasing age, and the regression coefficients were not different between groups (t = -0.89, df = 1, p = 0.3746) (Figure 3.2). Duration of illness was not a significant covariate after controlling for the effect of age. The MMN amplitudes at individual electrodes and their effect sizes are shown in Table 3.2. The largest effect size was seen at electrode FCz. The midline analysis showed more negative MMN frontally in both groups (electrode main effect: F(5,950) = 53.41, p < 0.0001, ε = 0.3245). MMN peaked at FCz in control group and at Fz in schizophrenia group. MMN at frontal electrodes was not correlated with any neuropsychological tests or PANSS scores.

3.3.3 Prediction model

MMN at frontal electrodes was not correlated with any neuropsychological tests (Table 3.3) or PANSS scores. Table 3.4 showed the multiple logistic regression model to predict from which group a subject came. The weighted combination of four factors, MMN amplitude at FCz, block design, arithmetic and performance IQ, could best differentiate the patient group from the control group and fit the observed data well. When using MMN amplitude as the only predictive factor, the percentage of concordant pairs was only 70.0%, and the adjusted generalized R^2 was only 0.17.

3.4 Discussion

Our study confirmed MMN deficit of schizophrenia in a Han Chinese population. In concordance with previous studies, duration MMN declined with aging in both schizophrenia patients and controls (Todd et al., 2008; Kiang et al., 2009). Since the baseline MMN amplitude is smaller in schizophrenia patients, the slower declination rate

could be due to the “floor effect” (Kiang et al., 2009). Interestingly, the aging effects on MMN were reported to be related to the length of inter-stimulus interval. Compared with younger subjects, elder subjects had significantly attenuated MMN when the inter-stimulus intervals were 4.5 seconds. The aging effects were not evident when inter-stimulus intervals were only 0.5 seconds (Pekkonen et al., 1996). Duration of illness and the chlorpromazine-equivalent dose were uncorrelated with duration MMN after correcting for age.

MMN was not correlated with any of the neuropsychological tests. Several studies have explored the correlation between MMN and neuropsychological tests in small samples of subjects (see Table S1). WCST and CPT were generally uncorrelated with MMN indices, and only Toyomaki et al. reported the duration MMN mean amplitude to be associated with WCST perseverative errors (Toyomaki et al., 2008). It is noteworthy that different MMN paradigms and indices yielded different results. For example, Kawabulo et al. found that phonetic duration MMN was correlated with the Rey Auditory Verbal Learning Test, while tone duration MMN was not (Kawakubo et al., 2006). Baldeweg et al. found that the MMN memory trace effect, rather than MMN amplitude, was correlated with verbal digit span and pre-morbid verbal intelligence (Baldeweg et al., 2004).

The weighted combination of MMN and neuropsychological tests enhanced the diagnostic power to differentiate schizophrenia patients from controls. To the best of our knowledge, this is the first study to evaluate the combination of electrophysiological markers and cognitive function for diagnostic purposes. According to previous meta-analyses, the effect sizes of the selected predictors were 1.18 for Arithmetic, 0.46 to 0.84 for Block Design, 1.26 for Performance IQ, and 1.23 for duration MMN (Heinrichs & Zakzanis, 1998; Umbricht & Krljes, 2005; Dickinson et al., 2007). Digit symbol has

been reported to have the largest effect size, but it was not selected by the prediction model (Dickinson et al., 2007). There are several reasons why a covariate will be dropped from a prediction model. For example, it may have no effect on the response variable after adjusting for the effects of the other covariates. Further, the correlation of a variable with other covariates can result in collinearity and multicollinearity problems in the regression model.

Our prediction model gave each subject an estimated probability of having schizophrenia, which is unlike the traditional cut-off point method to assign subjects to categorical groups. The probabilistic nature made the prediction model a dimensional assessment, which is emphasized in the proposed Diagnostic and Statistics Manual, fifth edition ("DSM-5 Development," 2011). The new diagnostic system recognizes cognitive impairment as an important symptom of schizophrenia. However, cognitive impairment is not included as criteria A symptom due to the lack of diagnostic specificity. For example, Bora et al. argued that the profiles, severity, relationship with clinical states, and prevalence of cognitive impairments do not help to differentiate schizophrenia from other major psychotic disorders. Further, early intellectual declination of cognition exists in a small portion of patients with schizophrenia (Bora et al., 2010). Incorporating MMN into the “broad” cognitive assessment could therefore be valuable. MMN impairment is relatively specific to schizophrenia. Abnormal MMN has not been observed in patients with bipolar affective disorder, major depressive disorder or schizoaffective disorder (Catts et al., 1995; Umbricht et al., 2003). In addition, MMN and neuropsychological tests are independent and measured by different constructs. A combination of cognitive measures with MMN may thus enhance the differential ability and better address the heterogeneous nature of schizophrenia.

There are several limitations of this study. First, only schizophrenia patients and healthy subjects were compared. The enhanced diagnostic specificity should also be evaluated by comparing schizophrenia to other major psychotic and affective disorders. Second, the subjects were mainly chronic schizophrenia patients, and the results may not be readily applied to first-episode or prodromal subjects. Third, the validity and reliability of the prediction model should be tested in another independent sample. Fourth, all patients in this study were taking psychotropic agents. It could be possible that the prediction model worked by differentiating subjects taking or not taking psychotropic agents, but not subjects with or without schizophrenia. Drug challenge studies in healthy subjects showed that benzodiazepines increased MMN latency (Rosburg et al., 2004) and decreased MMN amplitudes (Nakagome et al., 1998), and selective serotonin reuptake inhibitors such as escitalopram increased the MMN amplitude (Oranje et al., 2008). Dopaminergic agents did not influence MMN (Leung et al., 2007). In schizophrenia patients, treatment with antipsychotic agents (Schall et al., 1998; Umbricht et al., 1998, 1999; Shinozaki et al., 2002; Korostenskaja et al., 2005)[15-19] or benzodiazepines (Kasai et al., 2002; Murakami et al., 2002) had no effect on MMN, hence the MMN deficit in schizophrenia may not be the result of medications. Further, the second-generation antipsychotics have modest effects on improving cognitive function (Keefe et al., 1999; Woodward et al., 2005; Hill et al., 2010), in contrast to the first-generation antipsychotics have no or even adverse cognitive effects (Hill et al., 2010). Therefore, drug effects seemed to have little influence on the prediction model and the group difference of MMN.

In summary, MMN deficit was a robust phenomenon for Han Chinese schizophrenia patients, and duration MMN decline with increasing age in both schizophrenia patients and healthy subjects. A combination of electrophysiological and

neurocognitive markers better differentiated schizophrenia patients from healthy subjects. The multivariate phenotype approach delineated the heterogeneous nature of schizophrenia. As a measurement with good specificity for schizophrenia, future studies should evaluate the value of duration MMN in developing composite diagnostic batteries.

3.5 Tables and Figures

Table 3.1 Demographic data and clinical correlates.

Characteristics	Control	Schizophrenia	*P* value
Female – no. (%)	46 (60.5)	62 (51.7)	0.241
Age – years	36.25±1.12	37.96±9.83	0.264
Education – years	15.73±3.52	13.08±2.84	<0.001*
Smoking – PPD	0.048±0.20	0.17±0.41	0.016*
CPT			
d′	−0.03±1.06	−0.68±1.20	<0.001*
md′	−0.08±0.99	−0.90±1.32	<0.001*
WCST			
Perseverative errors	−0.13±0.95	0.78±1.43	<0.001*
Categories achieved	0.37±1.05	−0.50±1.04	<0.001*
Trials to complete first category	0.04±0.91	0.47±1.19	0.010*
Conceptual level response	0.26±1.05	−0.62±1.15	<0.001*
WAIS-III			
Arithmetic	11.96±3.15	8.22±3.23	<0.001*
Digit Span	12.38±3.14	9.76±4.15	<0.001*
Information	11.99±2.92	10.07±3.23	<0.001*
Digit Symbol-coding	11.90±2.92	10.46±12.81	0.350
Block Design	11.86±2.88	10.03±6.87	0.034*
Working Memory Index	112.14±15.30	92.10±17.57	<0.001*
Verbal IQ	112.67±16.22	94.53±17.08	<0.001*
Performance IQ	113.06±16.56	90.61±16.84	<0.001*
Full Scale IQ	112.25±18.88	92.52±15.63	<0.001*

*Significant difference between controls and patients with schizophrenia (significant level at 0.05)Independent *t* test for continuous variables.
Pearson's chi-square (2-sided) test for categorical variables.
PPD: package per day.
d′: sensitivity index of undegraded CPT.
md′: sensitivity index of degraded CPT.

Table 3.2 Comparison of mismatch negativity amplitudes between groups. Effect size was the standardized mean difference between groups (Cohen's d).

	Control	Schizophrenia	t value	*P* value	Effect size
Fp1	-0.45±0.51	-0.2±0.39	3.89	< 0.001	0.55
Fp2	-0.48±0.57	-0.21±0.47	3.63	< 0.001	0.52
F7	-0.3±0.48	-0.16±0.41	2.16	0.032	0.31
F8	-0.23±0.76	-0.09±0.63	1.4	0.163	0.21
Fz	-0.96±0.94	-0.41±0.69	4.71	< 0.001	0.66
F3	-0.82±0.86	-0.34±0.63	4.49	< 0.001	0.63
F4	-0.9±0.88	-0.39±0.64	4.76	< 0.001	0.66
FT7	-0.18±0.54	-0.09±0.45	1.24	0.216	0.18
FT8	-0.12±0.74	-0.07±0.48	0.59	0.559	0.09
FC3	-0.87±0.90	-0.36±0.67	1.79	0.004	0.63
FC4	-0.99±0.93	-0.41±0.66	5.1	< 0.001	0.7
FCz	-1.06±1.03	-0.39±0.76	5.21	< 0.001	0.72
T3	-0.003±0.48	0.007±0.53	0.13	0.900	0.02
T4	0.09±0.80	0.02±0.56	0.71	0.482	0.1
T5	0.16±0.81	0.13±0.67	0.3	0.765	0.04
T6	0.29±0.66	0.18±0.69	1.08	0.280	0.16
C3	-0.83±0.87	-0.33±0.69	4.44	< 0.001	0.62
C4	-0.88±0.88	-0.4±0.67	4.32	< 0.001	0.61
Cz	-0.96±1.01	-0.36±0.75	4.8	< 0.001	0.67
TP7	0.22±0.58	0.12±0.64	1.08	0.279	0.16
TP8	0.25±0.64	0.14±0.63	1.25	0.214	0.18
CP3	-0.64±0.80	-0.29±0.69	3.2	0.002	0.46
CP4	-0.68±0.85	-0.29±0.67	3.6	< 0.001	0.51
CPz	-0.75±0.95	-0.31±0.73	3.61	< 0.001	0.51
P3	-0.43±0.78	-0.18±0.67	2.41	0.017	0.35
P4	-0.43±0.81	-0.21±0.65	2.12	0.036	0.31
Pz	-0.5±0.86	-0.22±0.71	2.44	0.016	0.23

A1	0.44±0.48	0.19±0.59	3.04	0.003	0.44
A2	0.49±0.48	0.25±0.58	2.96	0.003	0.43
O1	0.1±0.58	0.08±0.75	0.17	0.865	0.03
O2	0.13±0.63	0.07±0.75	0.62	0.535	0.09
Oz	0.06±0.66	0.07±0.76	0.08	0.934	0.01

Table 3.3 Correlation between MMN and neuropsychological Tests.

	MMN mean amplitude at Fz	
Neuropsychological tests	**Correlation coefficient**	***P* value**
d'	−0.003	0.963
md'	0.023	0.758
Perseverative errors	−0.098	0.188
Conceptual level response	0.101	0.173
Categories achieved	0.067	0.364
Trials to complete first category	0.028	0.703
Arithmatics	0.046	0.545
Digit span	0.023	0.761
Information	0.061	0.430
Digit symbol	−0.079	0.304
Block design	−0.035	0.644
Working memory index	0.082	0.284
Verbal IQ	0.091	0.236
Performance IQ	0.094	0.219
Full IQ	0.059	0.443

Pearson's partial correlation, controlling for age and affected status.

Table 3.4 Multivariate predictive logistic regression model for schizophrenia

Covariate	Estimate	Standard Error	Wald Chi-square	*P* value	Odds ratio	95% Confidence Interval
Intercept	12.41	2.11	34.64	<0.001	-----	-----
FCz	1.10	0.28	15.20	<0.001	3.01	1.73–5.24
Arithmetic	−0.29	0.09	10.46	0.001	0.75	0.63–0.89
Block design	0.39	0.14	8.04	0.005	1.48	1.13–1.94
Performance IQ	−0.12	0.03	18.56	<0.001	0.88	0.84–0.94

Multiple logistic regression model: $n = 174$, percentage of concordant pairs = 90.5%, percentage of discordant pairs = 9.3%, percentage of tied pairs = 0.1%, adjusted generalized $R^2 = 0.61$, Deviance goodness-of-fit test $p = 0.985 > 0.05$ (df = 169), Pearson goodness-of-fit test $p = 0.534 > 0.05$ (df = 169), and Hosmer and Lemeshow goodness-of-fit test $p = 0.816 > 0.05$ (df = 8).

The estimated probability of having schizophrenia (i.e., the *predicted value*, $\hat{P}_i$) can be calculated using the following formula (FCz is the mean mismatch negativity amplitude at electrode FCz; Arithmetic, Block Design, and Performance IQ are test scores of WAIS-III):

$$\hat{P}_i = \frac{1}{1+\exp[-(12.41+1.10\times FCz-0.29\times \text{Arithmetics}+0.39\times(\text{Block design})-0.12\times(\text{Performance IQ}))]}$$

Figure 3.1 Grand average mismatch negativity waveforms.
(A) Grand average mismatch negativity waveform at each electrode shown for schizophrenia patients (red line) and healthy subjects (blue line). The mismatch negativity waveform reversed in polarity at the mastoid electrodes.
(B) Grand average MMN waveform at electrode Fz.
(C) Grand average MMN waveform at electrode FCz.

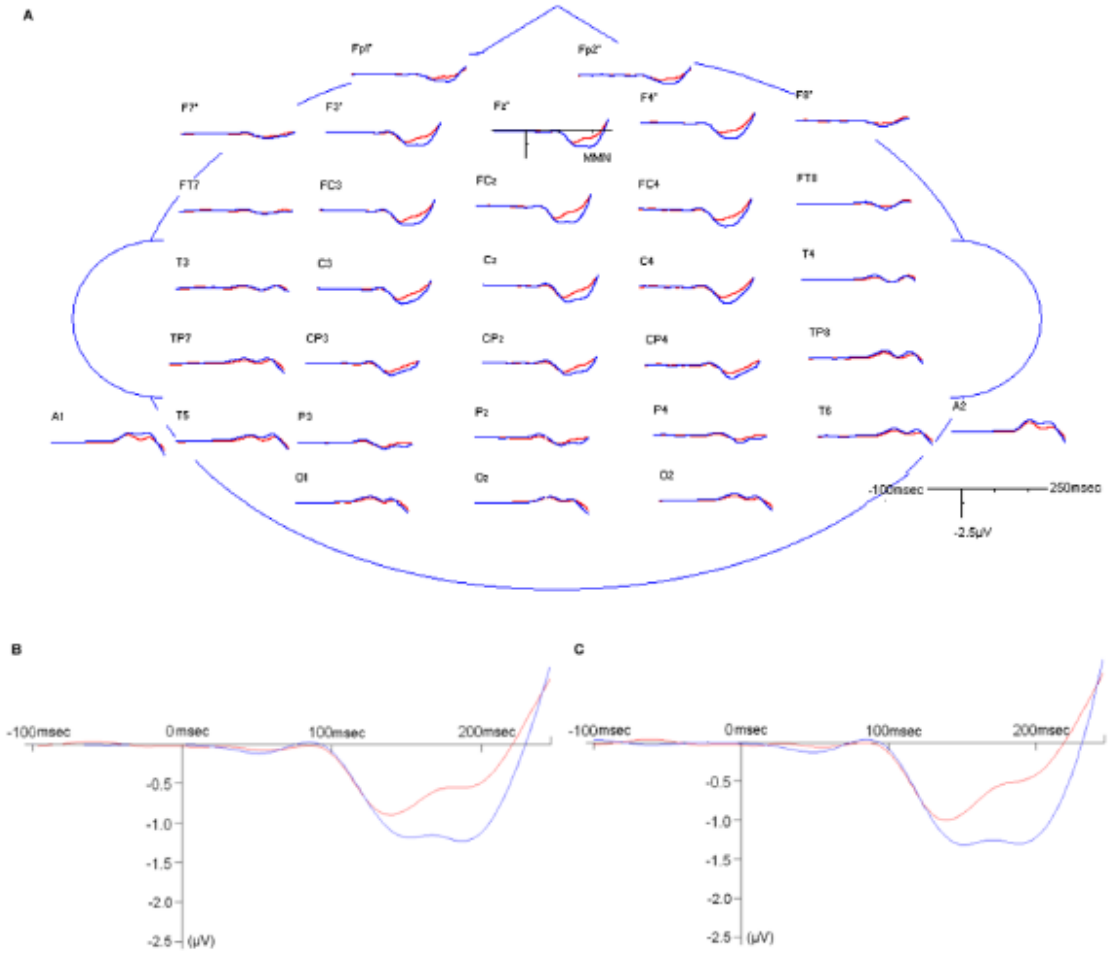
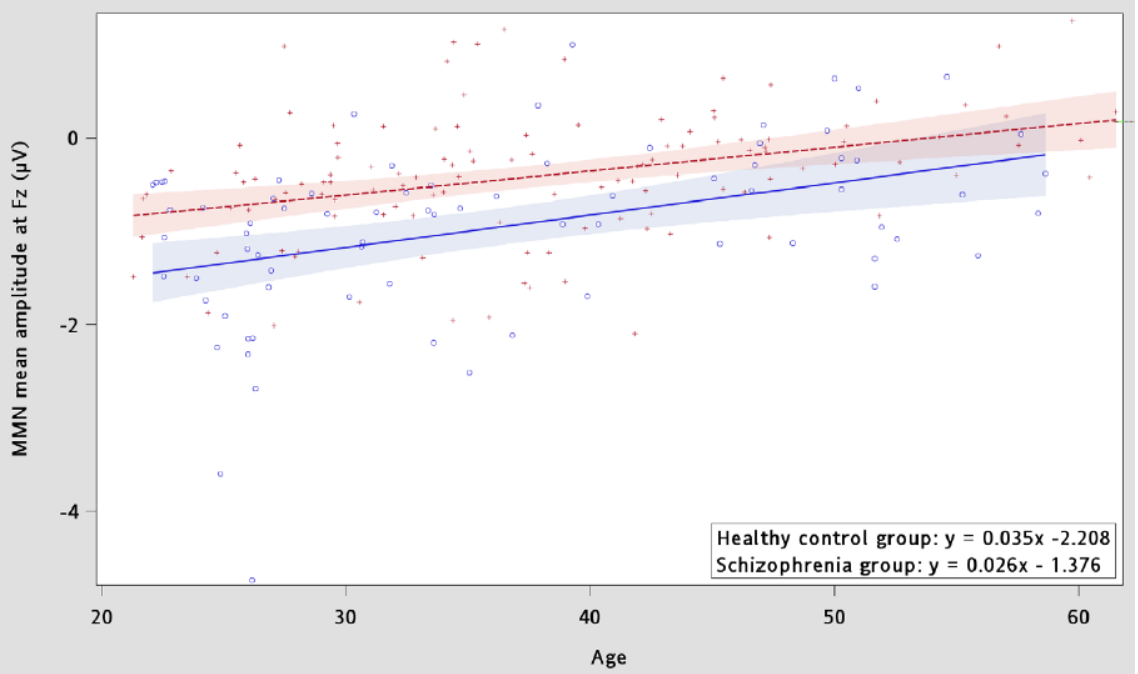


Figure 3.2 Effects of age on mismatch negativity. Mean mismatch negativity amplitude (135–205 msec) at electrode Fz reduces with aging. The reduction rate were not significantly different between healthy control group (open circles and solid regression line) and schizophrenia group (crosses and dashed regression line).



Chapter 4. Auditory Event-related Potential of Subjects with Suspected Pre-psychotic State and First Episode Psychosis

4.1 Introduction

Schizophrenia is a disorder of the brain that involves several levels of deficits (Braff & Light, 2004; Rissling & Light, 2010a, 2010b). Most neurobiological studies of schizophrenia have been conducted in chronic patients; however, the long duration of illness per se could be a confounder, making the interpretation of neurobiological findings rather difficult (Mathalon et al., 2000; Premkumar et al., 2008; Tanskanen et al., 2010). Also, the long-term use of antipsychotics has profound effects on brain neurochemistry and possibly brain morphology (Breier, 2004). A promising approach to explore the complicated pathogenesis of schizophrenia without being confounded by these factors is to monitor the progression of subjects from a pre-psychotic state to a full-blown psychotic episode (Cornblatt et al., 2003; Keshavan et al., 2011).

In the past decade, researchers worldwide have conducted prospective studies in this regard, but the majority of them focused on the ultra-high risk or late-prodromal state (Breier, 2004; Olsen & Rosenbaum, 2006), while little is known about what happened prior to ultra-high risk state. Keshavan et al. proposed the concept of early/broad at-risk mental states (E-BARS) to suggest needs to explore individuals at an earlier stage and broader range of at-risk mental states (Keshavan et al., 2011). In Taiwan, a study on the psychopathological progress of the pre-psychotic state (the SOPRES study) was initiated in 2006. In addition to including ultra-high-risk subjects who demonstrated a significantly higher probability of transition to a full-blown psychotic episode, the

SOPRES study also recruited subjects at marginal-risk (subjects presenting with non-specific cognitive and affective symptoms did not yet meet any diagnostic category), intermediate risk (subjects with schizotypal-like and some negative symptoms), and first episode psychosis(Liu et al., 2010; Liu et al., 2011). Thus the SOPRES data allows us to explore individuals putatively at pre-psychotic state while not reaching the severity of ultra-high risk criteria.

Auditory event-related potentials (ERP), including P50, N100, and mismatch negativity (MMN), have been utilized to study normal versus defective information processing in schizophrenia (Adler et al., 1982; Nagamoto et al., 1991; Clementz et al., 1997; Michie, 2001; Keshavan et al., 2008). Sensory gating methods using paired-click paradigm (Nagamoto et al., 1989; Nagamoto et al., 1991) had provided strong relationship between genes and the pathophysiological aspect of the illness (Freedman et al., 1997). They have also been identified as candidate endophenotypes of schizophrenia in order to reveal possible schizophrenia genes (Turetsky et al., 2007; Turetsky et al., 2008; Rissling & Light, 2010a). Several studies have investigated the relationship of auditory ERP components in high-risk subjects. For example, P300 amplitude reduction has been correlated with an increased vulnerability to psychosis(Bramon et al., 2008; Frommann et al., 2008; Ozgurdal et al., 2008; van Tricht et al., 2010). MMN amplitudes of prodromal subjects were found to be at an intermediate stage between those of the control and schizophrenia subjects, although the difference did not reach statistical significance (Brockhaus-Dumke et al., 2005). P50 and N100 were found with marginal differences between healthy control subjects and high-risk groups in P50 ratio (S2/S1) and N100 difference (S1-S2), while no significant differences in any parameter between converters and non-converters (i.e. at-risk subjects vs. truly prodromal patients) (Brockhaus-Dumke et al., 2008).

As compared with other studies that recorded ERPs solely in ultra-high-risk subjects or drug-naïve genetically high-risk probands, this study concurrently investigated the auditory ERPs of subjects at different levels of clinical severity, from normal controls to an early/broad at-risk mental state, ultra-high risk state, and first episode psychosis. Also an addition to previous studies on UHR subjects, we examined the intercorrelation between P50, N100, and MMN, explored the features of P50, N100, and MMN among these clinical subgroups, and compared the baseline ERP findings between the converters and non-converters of our ultra-high-risk subjects.

4.2 Methods

4.2.1 Participants

Subjects were participants in the SOPRES study who agreed to receive electrophysiological assessments. The rationale and methodology for the SOPRES study have been described elsewhere (Liu et al., 2010; Liu et al., 2011). Briefly, individuals presenting with “non-specific Cognitive deficits, Affective symptoms, Social Isolation, and School failure” (CASIS) (Cornblatt et al., 2003)or having newly developed psychotic-like symptoms were referred for assessment. The SOPRES study was approved by the National Taiwan University Hospital (NTUH) Institute Review Board. All subjects and/or their parents provided signed written informed consent before their participation in this study.

Originally, the levels of clinical severity were categorized into four groups by employing the Thought/Perception Diagnostic Interview Schedule (TP-DIS)(Liu et al., 2011). The group of first-episode psychosis (FEP) included participants with schizophrenia, schizophreniform disorder, brief psychotic disorder, or schizoaffective disorder meeting the DSM-IV criteria in the preceding one year. The ultra-high-risk

group (UHR) included participants with attenuated psychotic symptoms (APS) or brief limited intermittent psychotic symptoms (BLIPS)(McGorry et al., 2003). The intermediate-risk group (IRG) included participants who presented with odd thinking, feelings, speech, or perceptual experiences, which were not as severe as in the UHR group but met the criteria of schizotypal disorder according to the 10th edition of the International Classification of Diseases (ICD-10) without the duration requirement of two years. The marginal-risk group (MRG) included participants with CASIS symptoms (Cornblatt et al., 2003) without meeting either the threshold for the IRG or other diagnostic category. A group of age- and gender-matched healthy volunteers were also recruited. Of note, in our SOPRES 2-year follow-up, only one third of patients from the UHR group have converted into full-blown psychosis while none of the IRG and MRG subjects converted, and in our preliminary analysis, either from eyeballing the scatter plots or statistically tested, there is no significant distinction between these 2 groups in terms of the results of our interests, thus we combined these two groups to be an analogue of the recently proposed “early/broad at-risk mental states” (E-BARS) in later analyses.

Subjects with an IQ below 70, aged younger than 16 years, with a history of traumatic brain injury, a history of central nervous system illness, a prior psychotic episode lasting for more than one year, or current use of psychoactive stimulants were excluded. The pre-psychotic subjects who developed first-episode psychosis during the 2-year follow-up were defined as converters. In this study all converters came from the UHR group, while none of the E-BARS subjects converted to FEP.

4.2.2 Experimental procedures

Audiometry testing was used to exclude subjects who could not detect 40-dB sound pressure level tones at 500, 1000, and 6000 Hz presented to either ear. A standard protocol for auditory P50 and MMN paradigm was followed (Lijffijt et al., 2009; Light et al., 2010;

Shan et al., 2010) . The participants had not smoked for at least 1 hour before sessions (Adler et al., 1992; Olincy & Martin, 2005), and were asked to lie down in the supine position in a comfortable recliner in a sound attenuating, electrically shielded booth and instructed to relax with his/her eyes open and to focus on a fixation point (P50 and N100 session) or a cartoon running with no sound on the video monitor (MMN session).

The EEG signals were recorded with a Quik-Cap (Compumedics Neuroscan, El Paso, TX, USA) from 32 scalp locations (10-20 system). The auditory stimuli were generated by a Neuroscan STIM system, and data were recorded on a Neuroscan ACQUIRE system (Compumedics Neuroscan, El Paso, TX, USA). Stimuli were digitized at a rate of 1 kHz and an on-line band-pass filter at 0.5-100 Hz, without 60-Hz notch filter applied. Electrodes placed at the tip of the nose and at Fpz served as the reference and ground, respectively. Four additional electrodes were located above and below the left eye and at the outer canthi of both eyes to monitor blinks and eye movements. Electrode impedances were kept below 5 kΩ prior to recording.

Auditory ERPs were presented to the subjects binaurally via foam insert earphones in two consecutive sessions, i.e. the session of paired-click paradigm for P50/N100 followed by the duration MMN session. On-line averaging was used to monitor the number of trials free from gross artifacts (defined as activities exceeding ± 100 μV in the -100~500 msec time-window following stimuli). Regarding the pair-click P50/N100 paradigm, paired auditory clicks (1 msec, 85 dB) were presented every 8~12 seconds through the whole test session (average: 10 sec), with a 500-msec inter-stimulus interval (Clementz et al., 1998; de Wilde et al., 2007). The paired-click P50/N100 session was terminated when a minimum of 120 artifact-free trials had been obtained, which took about 30 minutes. For the duration MMN paradigm, pure tone stimuli (1 kHz, 85 dB SPL, 5 ms rise/fall, Hanning window) were generated by the Neuroscan STIM system. The

auditory stimuli consisted of standard stimuli (90%, 50-msec duration) and deviant stimuli (10%, 100-msec duration) delivered in a pseudo-random order with the constraint that deviant stimuli could not be repeated back-to-back. The cartoon soundtrack was turned off and replaced by the experimental auditory stimuli which were presented at a fixed 500-msec onset-to-onset asynchrony. The MMN session was continued until a minimum of 225 artifact-free deviant trials had been collected on line, which took approximately 30 minutes.

4.2.3 Data processing

All data were processed using Neuroscan Edit 4.3 software (Compumedics Neuroscan, El Paso, TX USA) by researchers who were blind to the subject's group(Boutros, 2008). Semi-automated procedures using the Tool Command batch processing Language (TCL) , began with EOG artifact reduction through a built-in pattern-recognition algorithm(Semlitsch et al., 1986). For paired-click P50/N100 continuous files, the data were epoched for the time window -100 to 923 msec relative to the first click, in order to cover both S1 and S2 in the same epoch. All epochs containing activities exceeding ± 50 μV were excluded and the epochs were then averaged and digitally bandpass-filtered (10 to 50 Hz for P50, 1 to 50 Hz for N100) in the frequency domain to prevent temporal aliasing(Boutros et al., 2004). Trials with artifacts were detected manually and rejected from further analysis. Thereafter, all peaks and preceding troughs were detected automatically at the Cz electrode using preset intervals (Clementz et al., 1998; Niznikiewicz et al., 2004; Brockhaus-Dumke et al., 2008; Light et al., 2010). Data from the subjects where the S1 amplitude (P50, N100) was less than 0.5 μV were removed from analysis (Nagamoto et al., 1989; Boutros, 2008). The P50 peak was defined as the largest positive deflection between 45 and 75 msec post-stimulus, and

its amplitude was assessed as the difference between this peak and the preceding negative trough (not earlier than 30 msec post-stimulus). The N100 component was identified as the most negative deflection within 80 to 150 msec post-stimulus, and N100 amplitude was defined as the absolute difference between the N100 peak and the preceding positive trough. In addition, if the stimulus 2 (S2) response could not be found within the 10 msec window for P50 or 20 msec for N100 of the latency of the S1 response, the S2 response was scored as 0 (Nagamoto et al., 1989; Boutros et al., 2004). P50 and N100 parameters included the S1 amplitude, S2 amplitude, amplitude difference (S1–S2), and P50/N100 gating ratio (S2/S1). A maximum of 2 for gating ratio was used to prevent outliers from disproportionately affecting the group means (Nagamoto et al., 1989).

For duration MMN analysis, each subject's continuous data files after EOG artifact reduction were then epoched 100 msec pre-stimulus to 500 msec post-stimulus. Following linear detrending and baseline correction to the average pre-stimulus interval, all epochs containing amplitudes exceeding ± 50 μV in frontal recording sites (F7, F8, Fp1, Fp2, F3, F4, and Fz) were automatically rejected (Wynn et al., 2010). EEG responses to standard and deviant stimuli were separately averaged to create a standard ERP and a deviant ERP, and both were low-pass filtered at 20 Hz (0-phase shift and 24-dB/octave roll-off) to remove any residual high-frequency artifacts. MMN waveforms were generated by subtracting the standard ERP from the deviant ERP. MMN indices were measured as the mean voltage from 135 to 205 milliseconds from the Fz electrode (Michie et al., 2002; Light et al., 2010; Wynn et al., 2010).

4.2.4 Statistical analyses

For demographic characteristics, we used analyses of variance and chi-square tests (or Fisher's exact tests if necessary) to compare continuous and categorical variables

across different risk groups and normal controls, respectively. The correlations between ERP parameters were examined using the Spearman rank correlation tests. Analyses of variance with post-hoc analyses were used to examine differences in ERP parameters among these four groups. Treating the risk level as a continuous covariate, linear trends of ERP parameters across these four groups were checked by regression models. A subgroup analysis of participants within the UHR group was performed to determine factors associated with converting to full-blown psychosis or not. Demographic characteristics, SOPS symptom dimensions (i.e. positive, negative, disorganized and general symptoms) and ERP parameters were compared between converters and non-converters. Chi-square or Fisher's exact tests were used for categorical variables, while nonparametric Mann-Whitney U tests were used for continuous variables because of the small sample size for converters and non-converters in the UHR group. All tests were 2-sided with $\alpha = 0.05$.

4.3 Results

In total, we recruited 99 clinical subjects, including 32 FEP, 30 UHR, 37 E-BARS, along with 56 normal controls (Table 4.1). There were no significant differences in age, gender, education, and smoking status. Only the UHR and FEP subjects were prescribed with antipsychotics.

Regarding the relationship between individual ERP indicators, the Spearman's rank correlation coefficients are outlined in Table 4.2. The majority of P50 and N100 parameters were mutually correlated, except no correlation existed between N100 ratio and any P50 parameter. MMN was correlated with neither P50 nor N100 parameters.

With respect to the differences in ERPs between these four subgroups (Table 4.2), only MMN reached statistical significance ($p = 0.019$). In post hoc analyses, there were

significant differences in MMN in the E-BARS (p = 0.007), UHR (p = 0.035), and FEP (p = 0.035) groups as compared to the controls.

Figure 4.1 demonstrates linear trends of P50 ratios (S2/S1) and the N100 differences across different risk groups (P50 ratios, p=0.060; N100 differences, p=0.018); that is, these two sensory gating indicators were largest in the FEP group followed by the UHR group, the E-BARS group and the normal controls in order. Grand average MMN waveforms for the FEP patients (in blue) and control subjects are shown in Figure 4.2. The MMN waveform reversed in polarity at the mastoid electrodes.

Further analysis for participants within the UHR group showed no significant differences between converters and non-converters in either demographic profile or any of the four symptom dimensions (Table 4.4 and Figure 4.3). There was some evidence suggesting that the converters had a poorer performance than the non-converters in several P50 and N100 indicators including P50 gating ratio (p = 0.099), N100 gating ratio (p = 0.060), N100 difference (p = 0.088), and N100 S2 amplitude (p = 0.060), but not MMN.

4.4 Discussion

To the best of our knowledge, this study is one of the first to examine auditory ERPs (P50/N100/MMN) in not only subjects with first-episode psychosis (FEP) and ultra-high-risk (UHR) subjects, but also in those with presumed early/broad at-risk mental states (E-BARS). In general, MMN was correlated with neither P50 nor N100, whereas many parameters of the latter two were inter-correlated with each other. Specifically, as compared to healthy controls, all three clinical groups, i.e. E-BARS, UHR and FEP had significantly lower MMNs. On the other hand, the differences in P50 and N100 between control and clinical groups were not significant, while a linear trend

of more deviance from controls across different levels of clinical severity was noticed in P50 ratios (S2/S1) and N100 differences (Figure 4.1). For subjects within the UHR group, certain P50 and N100 indicators might be useful when attempting to discriminate converters from non-converters.

Examining subjects with a gradient of clinical severities spanning from normal control, early at-risk state, ultra-high risk state to first episode psychosis is helpful to delineate the pathophysiological mechanisms throughout the formation of psychosis. Our results suggest that MMN and P50/N100 represent quite different inferences in the pathological information processing of subjects with at-risk mental status. This is in agreement with current knowledge that MMN reflects deviance detection which might be mediated by glutamate(Korostenskaja et al., 2007; Leung et al., 2007; Javitt et al., 2008; Korostenskaja & Kahkonen, 2009), while P50/N100 refers to sensory gating which is more likely related to dopamine and other neurotransmitters (Pekkonen et al., 2005; Hall, Schulze, Bramon, et al., 2006; Price et al., 2006; Turetsky et al., 2007; Javitt et al., 2008; Keshavan et al., 2008; Turetsky et al., 2009). The high correlations between N100 difference and P50 ratio and P50 difference was compatible with previous studies(Fuerst et al., 2007; Brockhaus-Dumke et al., 2008), suggesting “both P50 and N100 reflect stimulus registration in similar ways but gating or habituation to repeated stimulation in different ways”(Brockhaus-Dumke et al., 2008).

Our findings in duration MMN suggest it to be a trait, or a very sensitive marker, for schizophrenia, which means reduced MMN could be detected at subjects presenting with symptoms suggesting a putatively pre-psychotic state (Green et al., 2009; Atkinson et al., 2012), yet such a reduction might not get much worse along with the increase of clinical severity, especially in terms of emergence of attenuated psychotic symptoms. Previous studies have demonstrated impaired duration MMN in nonpsychotic biological

first-degree relatives of patients with schizophrenia (Michie et al., 2002) and reduced MMN in subjects at ultra-high risk state (Michie et al., 2002; Shin et al., 2009; Atkinson et al., 2012), and glutamate system dysfunction has been noted in at-risk mental state subjects (Stone et al., 2009). This study further revealed that even people at early/broad risk states might already demonstrate detectable MMN reduction.

In contrast to MMN, the parallels between the extent of sensory gating problems manifested by P50 gating ratio and N100 differences and the gradient of clinical severity suggest these two ERP indices might be state-dependent markers for schizophrenia. This might violate the definition of an ideal endophenotype (state-independent or symptom-independent). However, several studies have provided mixed results with regards to the relationship between P50 gating ratio and clinical presentations (Ringel et al., 2004; Louchart-de la Chapelle et al., 2005), between clinical high-risk and genetic high-risk (Myles-Worsley et al., 2004), as well as between different clinical stages (Brockhaus-Dumke et al., 2008). Nonetheless, our findings could provide new insights regarding the interpretation of such inconsistent findings. We conjecture that during pre-psychotic state when sensory-gating deficits are relatively mild, P50/N100 might be state-dependent markers as revealed by our findings; but once frank psychosis occurs and the sensory-gating problems become manifest, the severity of symptoms or duration of psychosis were less likely to have strong correlation with the extent of P50 deficits as revealed by a review of studies(Potter et al., 2006).

Based on our preliminary analysis, P50 and N100, rather than MMN, are potential candidates to differentiate converters and non-converters among subjects at ultra-high risk for schizophrenia, even though a recent study revealed reduced duration MMN associated with a higher risk of converting to first-episode psychosis among at-risk subjects (Bodatsch et al., 2011). Actually, among our UHR subjects, the mean MMN of

converters was indeed lower than non-converters (converter vs. non-converters = -.50 vs. -1.06) but this was not statistically significant. This could merely be an issue of statistical power because of the small sample size in this subgroup analysis (converters, N=6; non-converters, N=13). Further research about predicting conversion in UHR subjects by different indices of ERPs will be necessary to clarify this issue.

There are several limitations that are worth noting. The relatively small sample size limits our statistical power to detect smaller between-group differences. The validity of our clinical subgrouping of early/broad at-risk mental states is pending further follow-up and exploration. UHR and FEP subjects were not studied in an antipsychotic-free status; while use of antipsychotic might diminish the magnitude of P50 gating deficit hence masks some potential findings. In addition, we used data collected by midline electrodes to analyze the ERPs for consistency with previous literature and protocols, while the German Research Network on Schizophrenia Group used lateral electrodes to yield positive findings on prodromal studies (Frommann et al., 2008), thus topographic maps and source localization are factors to be considered when studying the ERPs underlying these high-risk subjects.

By employing the concept of E-BARS, this study provides new inferences about pre-attentional auditory event-related potentials, i.e. P50, N100 and MMN, in subjects across different risk levels of psychotic disorders, from early/broad at-risk mental state, ultra-high risk state, and first episode psychosis. Impaired deviance detection already exists in people at pre-psychotic state, regardless of clinical severity. On the contrary, sensory gating varies depending on different risk levels. A preliminary analysis showed some promising results for predicting conversion to psychosis. Further longitudinal research monitoring neurobiological changes of the same subjects at different levels of clinical severity are necessary to explore the underpinning pathogenesis.

4.5 Tables and Figures

Table 4.1 Demographic data of the four subgroups.

Variable	NC (n=56)	E-BARS (n=37)	UHR (n=30)	FEP (n=32)	Test statistics[a]	*P*-value[b]
Gender, n (%)					4.40	.222
Male	22 (39.3)	21 (56.8)	17 (56.7)	13 (40.6)		
Female	34 (60.7)	16 (43.2)	13 (43.3)	19 (59.4)		
Age, mean (SD), y	23.64 (6.37)	21.54 (3.45)	22.01 (3.79)	22.63 (4.56)	1.52	.210
Education, mean (SD), y	14.79 (2.85)	13.76 (2.07)	14.33 (2.11)	13.50 (2.48)	2.33	.076
Smoker, n (%)	5 (8.9)	3 (8.1)	5 (16.7)	3 (9.4)	1.649	.648

NC, normal control group; E-BARS, early/broad at-risk mental states; UHR, ultra-high risk group; FEP, first-episode psychosis group.
None of the NC and E-BARS subjects received antipsychotic treatment; in the UHR group, 8 were drug-naïve, 8 used aripiprazole ≤7.5 mg/day, 6 used sulpiride ≤200 mg/day, 4 took amisulpiride 200 mg/day, 3 used risperidone ≤3 mg/day, and 1 used quetiapine 100 mg/day, the majority of them received antipsychotic treatment for less than 3 months; in the FEP group, 6 were drug-naïve, 5 used olanzapine 5–10 mg/day, 10 used aripiprazole 3.75–22.5 mg/day, 4 used amisulpiride 100–400 mg/day, 5 used risperidone 2–4.5 mg/day, 2 used sulpiride 200 mg/day.

[a] ANOVA (analyses of variance) for age and years of education; Chi-square test for gender; Fisher's Exact test for smokers due to the expected number being less than five for at least 1 cell.

[b] *P*-values were 2-sided.

Table 4.2 The Spearman's correlation coefficients among P50, N100 and MMN Parameters. Number of subjects for P50/N100 was 152 and for MMN was 130.

	P50 S1	P50 S2	P50 ratio	P50 difference	N100S1	N100S2	N100 ratio	N100 difference	Age
P50 S1									−.089
P50 S2	.235**								−.117
P50 ratio	−.231**	.836**							−.057
P50 difference	.743**	−.405**	−.769**						.007
N100S1	−.573**	−.056	.223**	−.495**					−.059
N100S2	−.157	−.098	−.032	−.082	.192*				.153
N100 ratio	−.044	.073	.098	−.085	.154[c]	−.887**			−.154
N100 difference	.447**	−.019	−.239**	.429**	−.846**	.293**	−.609**		.104
MMN	.007	0.007	.011	.024	.127	.028	.038	−.122	.037

*p-value<.05, 2-sided; **p<.001, 2-sided.

Table 4.3 P50, N100 and MMN parameters among the four Subgroups [a]

P50	NC n=56 Mean (SD)	E-BARS n=35 Mean (SD)	UHR n=29 Mean (SD)	FEP n=32 Mean (SD)	Test statistics[b]	*P*-value[c]
Trials	112.4 (26.2)	111.8 (25.2)	102.83 (30.2)	112.2 (19.9)	1.05	.372
S1 latency (ms)	62.9 (8.1)	63.7 (7.8)	64.2 (6.6)	63.2 (9.0)	0.18	.909
S1 (μV)	2.37 (1.11)	2.49 (1.68)	2.29 (1.22)	2.19 (1.07)	.35	.791
S2 (μV)	.85 (.76)	1.04 (1.12)	1.06 (.73)	1.05 (.83)	0.61	.609
S2/S1 ratio	.40 (.41)	.47 (.48)	.55 (.45)	.58 (.57)	1.20	.313
S1-S2 (μV)	1.52 (1.13)	1.46 (1.22)	1.22 (1.30)	1.14 (1.30)	0.86	.464
N100						
S1 (μV)	−6.96 (3.83)	−6.20 (3.70)	−5.08 (2.58)	−5.36 (3.03)	2.52	.060
S2 (μV)	−1.59 (1.57)	−1.64 (1.88)	−1.10 (1.29)	−1.66 (1.44)	0.89	.447
S2/S1 ratio	.26 (.25)	.34 (.41)	.23 (.27)	.35 (.34)	1.34	.263
S2-S1 (μV)	5.37 (3.80)	4.56 (3.68)	3.99 (2.63)	3.70 (3.24)	1.95	.1244
MMN	n=53	n=30	n=19	n=28		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Fz (μV)	−1.37 (.89)	−.83 (.80)	−.88 (.92)	−.94 (.84)	3.46	.019[d]

NC, normal control group; E-BARS, early/broad at-risk mental states; UHR, ultra-high risk group; FEP, first-episode psychosis group. SD, standard deviation.

[a] Some subjects failed to stay before the ERP session was terminated.

[b] The test statistics were obtained by ANOVA (analyses of variance).

[c] *P*-values were 2-sided.

[d] Post-hoc analyses by independent *t* tests: Control versus E-BARS: $p=.007$, Control versus UHR: $p=.035$, Control versus FEP: $p=.035$.

Table 4.4 The comparison of clinical characteristics and ERP parameters in converters versus non-converters among ultra-high risk group. (n=30)

	Converter (n=11)	Non-converter (n=19)	Test statistics[a]	*P*-value[b]
Male/Female	7/4	10/9	.344	0.708
Smoker/Non-smoker	1/10	4/15	.718	0.626
	Mean (SD)	Mean (SD)	Test statistics[c]	*P*-value[d]
Age (years)	20.83 (3.07)	22.69 (4.07)	1.140	.254
Education (years)	13.91 (2.12)	14.58 (2.12)	0.881	.379
Symptom dimensions				
Positive	12.55 (3.08)	10.32 (3.97)	−1.596	.111
Negative	12.28 (8.31)	8.95 (6.40)	−1.122	.262
Disorganized	7.45 (4.66)	6.53 (5.22)	−0.691	.490
General	9.73 (4.58)	9.00 (5.13)	−0.497	.619
P50 parameters	Mean (SD) (n=11)	Mean (SD) (n=18)	Test Statistic[c]	*P*-value[d]
Trials	96.1 (37.4)	106.9 (25.1)	0.450	.653
S1 latency (ms)	64.27 (4.63)	64.11 (7.72)	0.315	.753
S1 amplitude (μV)	2.08 (.87)	2.41 (1.39)	0.360	.719
S2 amplitude (μV)	1.20 (.73)	.98 (.74)	−0.339	.735
S2/S1 ratio	.67 (.38)	.47 (.48)	−1.648	.099
P50 difference (μV)	.88 (.99)	1.43 (1.44)	1.348	.178
N100 parameters	Mean (SD) (n=11)	Mean (SD) (n=18)	Test Statistics[c]	*P*-value[d]
S1 amplitude (μV)	−4.60 (1.75)	−5.38 (2.99)	−0.405	.686
S2 amplitude (μV)	−1.67 (1.28)	−.75 (1.21)	1.884	.060
S2/S1 ratio	.35 (.29)	.16 (.23)	−1.884	.060
N100 difference (μV)	2.93 (1.69)	4.63 (2.92)	1.708	.088
MMN	Mean (SD) (n=6)	Mean (SD) (n=13)	Test Statistics[c]	*P*-value[d]
Fz (μV)	−.50 (.49)	−1.06 (1.04)	−1.316	.188

SD, standard deviation.
[a] Chi-square tests.
[b] *P*-values, 2-sided, were obtained by Fisher's exact test due to expected number less than five for at least 1 cell.
[c] Mann–Whitney U tests.
[d] Asymptotic *p*-values, 2-sided.

Figure 4.1 P50 ratios and N100 differences. The left panel demonstrates P50 ratio (S2 amplitude / S1 amplitude) and the right one N100 difference (μV; S2 amplitude–S1 amplitude) of individual participants. Larger ratio (S2/S1) and smaller difference (S1–S2) indicate poorer gating. The horizontal lines indicate the mean values within each risk group. CTL:control; E-BARS: early/broad at-risk mental states; UHR: ultra-high risk group; FEP: first-episode psychosis.

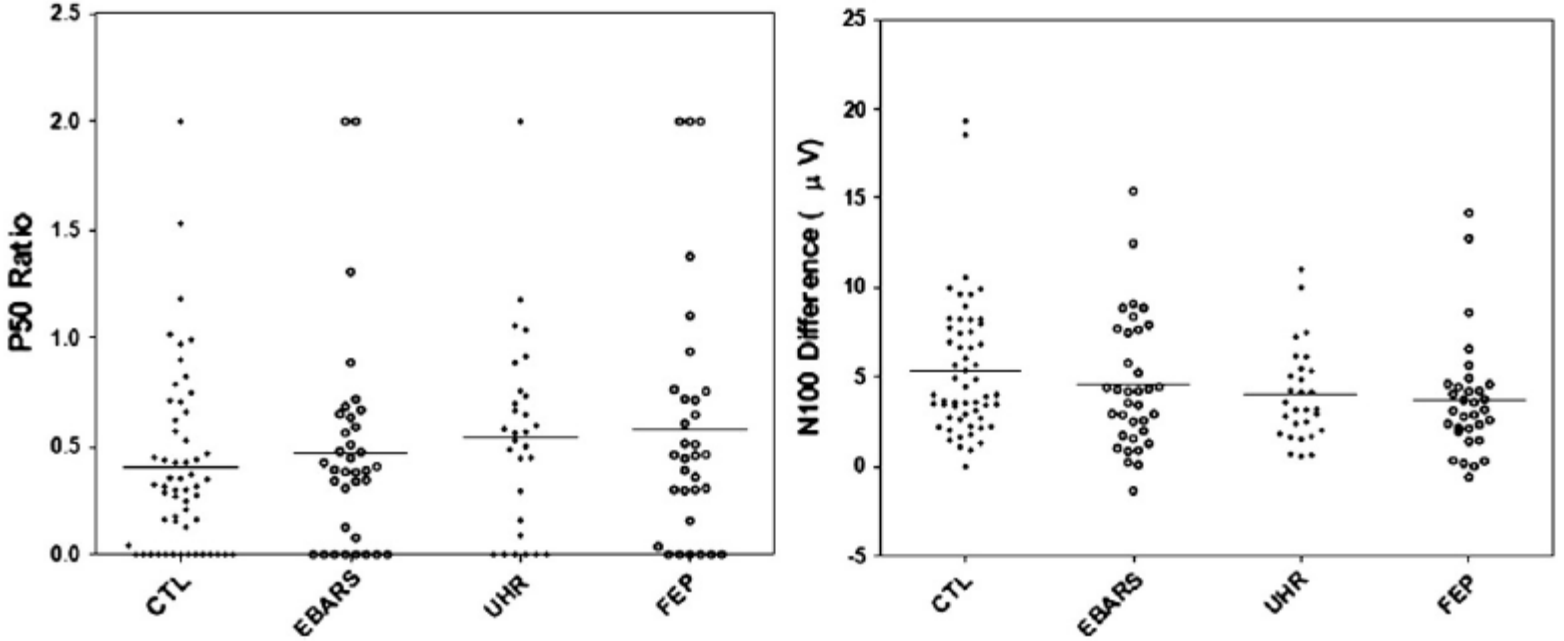


Fig. 1. P50 ratios and N100 differences. The left panel demonstrates P50 ratio (S2 amplitude / S1 amplitude) and the right one N100 difference (μV; S2 amplitude–S1 amplitude) of individual participants. Larger ratio (S2/S1) and smaller difference (S1–S2) indicate poorer gating. The horizontal lines indicate the mean values within each risk group. CTL: control; E-BARS: early/broad at-risk mental states; UHR: ultra-high risk group; FEP: first-episode psychosis.

Figure 4.2 Grand average mismatch negativity (MMN) waveforms for healthy control subjects (in blue) and (A) MRG, (B) IRG, (C) UHR, (D) FEP subjects (in red). Left and right columns indicate Fz and A1 (mastoid) electrodes. The MMN waveform reversed in polarity at the mastoid electrodes.

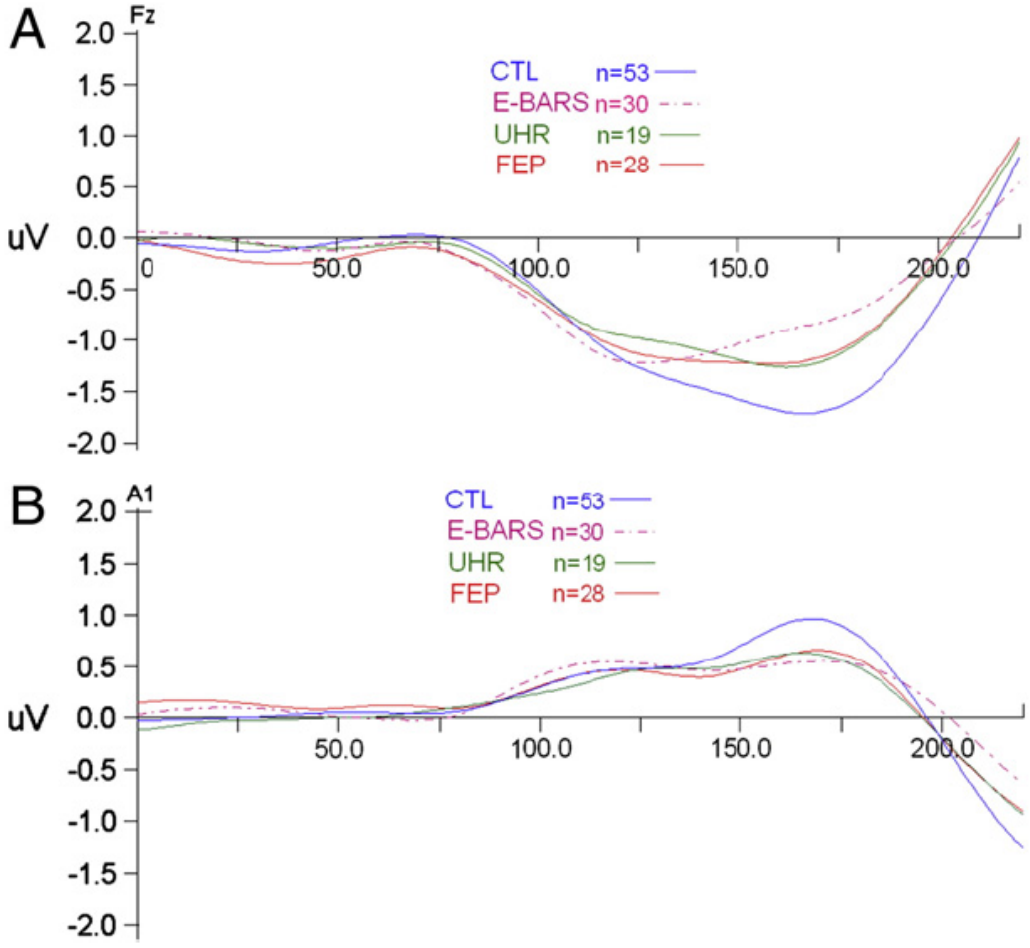
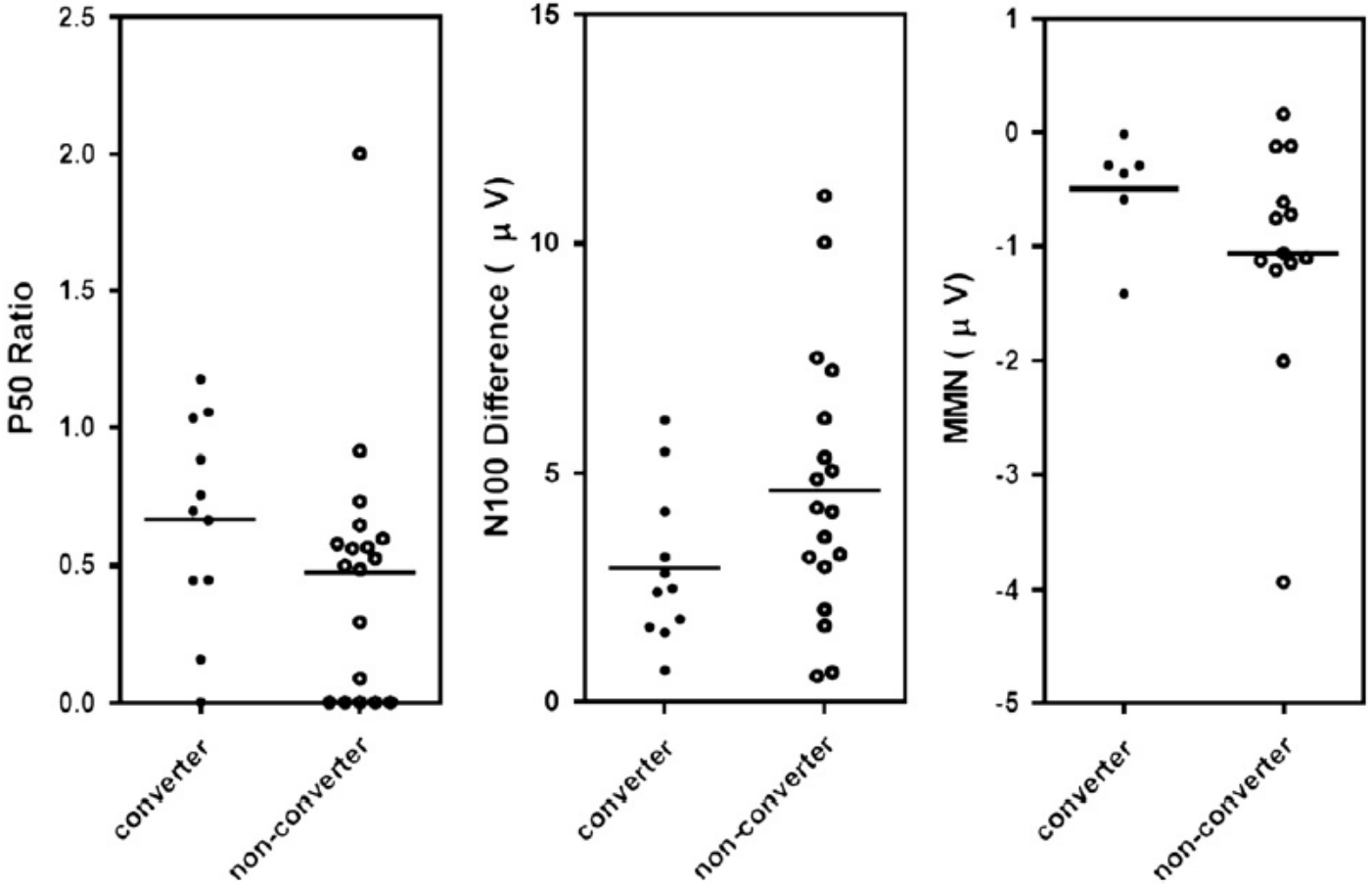


Figure 4.3 Three event-related potentials in non-converters versus converters within the ultra-high risk subgroup (UHR). The left panel shows P50 ratio (S2 amplitude/S1 amplitude), the middle one N100 difference (μV; S2 amplitude–S1 amplitude), and the right on MMN (μV) of UHR individuals. The horizontal lines denote the mean values.



Chapter 5. Time-Frequency Analysis of Mismatch Negativity in Schizophrenia Patients

5.1 Introduction

Schizophrenia is a major and chronic neuropsychiatric disorder. Neuroscience tools provide us more brain insights and have been one of the focuses of schizophrenia research in recent years(Blow, 2008; Javitt et al., 2008; Keshavan et al., 2008). For example, ERP (event-related potentials), in which a large number of time-locked experimental trials are averaged together, are used to investigate information processing in healthy versus schizophrenia subjects.

Among the ERP studies, many have convincingly demonstrated that patients with schizophrenia have robust deficits in auditory mismatch negativity (Turetsky et al., 2007; Javitt et al., 2008). The mismatch negativity, MMN, is elicited task-independently by an infrequently presented stimulus ("deviant" or “oddball”), differing from the frequently-occurring stimuli ("standards") in physical parameters such as duration, intensity, or frequency(Näätänen, 2003). Successful processing of sensory inputs requires the ability to facilitate responses to less frequent salient stimuli, while MMN indicates the measures of impaired deviance detection (Turetsky et al., 2007). It reflects an automatic and pre-attentional form of sensory processing, and has been proposed as candidate endophenotypes for schizophrenia (Braff & Light, 2004; Turetsky et al., 2007; Javitt et al., 2008; Keshavan et al., 2008).

However, the traditional event-related potential approach was established under the assumption that 1. single-trial EEG data time locked to some class of experimental events consists of an average ERP; 2. time course and polarity is fixed across the trials; 3. other

EEG processes whose time courses are completely unaffected by the experiment events. In fact, most oscillatory information in the EEG disappeared through signal averaging, and it has been challenged by the proposal that ERPs should not be regarded as uncorrelated with the background EEG, but are instead generated by event-related reorganization of this ongoing rhythmic activity (Delorme & Makeig, 2004). In contrast, contemporary time-frequency approaches represent changes in oscillatory activity as a function of time, and provide more information on underlying brain activity than the traditional ERP approach. For example, the open source toolbox “ERPWAVELAB” provides tools for visualization of the ERP with time-frequency methods (Morup et al., 2007).

This study tried to focus on event-related potential components such as mismatch negativity (MMN) between control and schizophrenia groups in Taiwan. In addition, this study also compared the time-frequency analysis with averaged event-related potentials of these event-related potentials.

5.2 Materials and Methods

5.2.1 Participants

We investigated 55 schizophrenia patients and 42 control subjects in this study. A simple hearing test over 500 Hz, 1000 Hz and 6000 Hz were conducted before the experiment to assure adequate hearing acuity of the participants. For the control participants, detailed evaluations were arranged to rule out any major medical problems, psychiatric diagnosis, head trauma, seizure and substance use history. All participants gave their informed consent before the experiment. The study was approved by the ethics committee of National Taiwan University Hospital (NTUH: 9461712119). Participants

were abstinent from smoking on the day of experiment to exclude the effect of nicotine on ERP (Knott et al., 2009). Please refer to Table 5.1 for the demographic data.

5.2.2 Experimental setup

The authors followed standard protocol for MMN to perform experimental paradigm and data processing (Light et al., 2010). Participants were seated in a comfortable recliner in a sound-attenuating, electrically shielded booth. The auditory stimuli were generated by Neuroscan STIM system and were presented to subjects binaurally via foam insert earphones. The data was recorded by Neuroscan ACQUIRE system (NeuroScan, Inc., El Paso, TX). The EEG signals were recorded with an electrode cap (Quik-Cap, NeuroScan, Inc., Charlotte, NC) from 32 scalp locations (10-20 system). Electrodes placed at the tip of the nose and at Fpz served as the reference and ground, respectively. Blinks and eye movement were monitored via EOG above and below the left eye, and outer canthi of both eyes. Impedance was kept below 5 kΩ. Signals were digitized at a rate of 1 kHz and a on-line band-pass filter at 0.5-100 Hz. During the test session, subjects were closely observed through a video monitor and EEG for signs of sleep or slow wave activity, which, if present, prompted the experimenter to speak briefly with the subject.

ERP were recorded in all the participants using auditory oddball paradigm for duration MMN. Participants were instructed to relax and avoid excessive blinking with his/her eyes open and viewed a benign cartoon film over the MMN session for approximately a 30-min period. The cartoon soundtrack is turned off and replaced by the experimental tones. To minimize eye movement, the cartoon film is presented at eye level on a 19-inch LCD monitor screen. The duration of standard stimulation (occupied 90% of total stimulation) and deviants stimulation (occupied 10% of total stimulation) were 50 msec and 100 msec respectively while they are in pseudorandom order. Stimuli

were presented at a fixed 500msec onset-to-onset asynchrony. During testing, online ERP averages to standard and deviant tones are also acquired to monitored signal quality and the number of sweeps free of gross artifacts (defined as ±100 μV across the -100~500 msec following stimuli). The MMN session was terminated when a minimum of 225 artifact-free deviant trials were collected.

5.2.3 EEG data processing

Semi-automating procedures using TCL (Tool Command Language) batch processing language, began with EOG artifact reduction through a built-in pattern-recognition algorithm (Semlitsch et al., 1986), were used for offline data analysis first. The subject's continuous data files were utilized for both standard averaging over the segments and time-frequency analysis (described below).

For traditional ERP averaging, the continuous data were epoched 100 msec pre-stimulus to 500 msec post-stimulus. EEG responses to standard and deviant stimuli were separately averaged to create a standard ERP and a deviant ERP, while MMN waveforms were generated by subtracting the standard ERP from the deviant ERP. Since problem regarding the measurement of peak ERP amplitude and latency has been raised, mean MMN amplitude across the 135 to 205 msec range from Fz electrode was compared between groups (Michie et al., 2002; Light & Braff, 2005a, 2005b; Light et al., 2010).

5.2.4 Time-frequency analysis

Each subject's continuous data files were first downsampled from 1000 Hz to 250 Hz. This reduced the size of data under the consideration of the original bandwidth of signal. EEGLab tool (http://sccn.ucsd.edu/eeglab/index.html) was then used for filtering(Delorme & Makeig, 2004). The filter setting was a band-pass filter with

passband of 1-80 Hz. A notch filter was also set at 60 Hz to reject the interference of noise. Thereafter we epoched data from -100 msec before stimulus onset to 500 msec after stimulus and set -100 msec to 0 msec as baseline. Removed baseline was performed in each epoch. Time-frequency analysis was performed using ERPwavelab (http://www.erpwavelab.org/) (Morup et al., 2007). Since MMN is typically measured at the Fz electrode, only the Fz channel was sent in further calculation (Niznikiewicz et al., 2004; Javitt et al., 2008; Light et al., 2010).

Complex Morlet wavelet were used to compute the time-frequency analysis for each epoch and explored the six parameters(Morup et al., 2007). These six parameters from ERPwavelab included: ERSP, WTav, avWT, induced activity, ITPC and ITLC, could be explained as follows:

ERSP (event related spectral perturbation): The measure of the average power over epochs. The calculation of ERSP is shown in the following:

$$\mathrm{ERSP}(c, f, t) = \frac{1}{N}\sum_{n}^{N}\left|X(c, f, t, n)\right|^2, \qquad (1)$$

where *X(c, f, t, n)* denote the time-frequency coefficient at channel *c*, frequency *f*, time *t* and epoch *n* of the signal given by *x(c, t, n)*. The ERSP represents event-related (which is dependent on the different auditory stimulation type) spectrum perturbation, it represents the spectrum of this particular event-related potential (ERP) which deviant from the baseline brain activity. As its calculation method from the formula, it related to the "distance" deviate from the baseline.

WTav: The measure of power in the average amplitude of the epochs which is denoted as

$$\mathrm{WTav}(c, f, t) = \frac{1}{N}\sum_{n}^{N}\left|X(c, f, t, n)\right|. \qquad (2)$$

The WTav represents mean waveform from all trials for this particular ERP, which may cancel out the out-phase activity in each trial, then take the wavelet transformation and display its magnitude of spectrum. The physiological meaning represents the spectrum of the in phase brain activity for this particular ERP in whole trials.

avWT: The mean power from each time-frequency transformed evoke potential in each epoch which is denoted as follows:

$$\text{avWT}(c, f, t) = \frac{1}{N}\sum_{n}^{N} X(c, f, t, n). \qquad (3)$$

The avWT represents take all trials' wavelet transform firstly then calculate their mean activity. The physiological meaning represents the mean sum spectrum of both in-phase and out-phases brain activity in whole trials.

Induced activity: The measure of non-phase locked activity. The induced activity represents difference between WTav and avWT, as shown in the following:

$$\text{INDUCED}(c, f, t) = \text{WT}av(c, f, t) - \left|avWT(c, f, t)\right|. \qquad (4)$$

This parameter could be used as the parameter of out-phase brain activity in ERP.

ITPC (inter-trial phase coherence): The measure of phase consistency over epochs which is denoted as follows:

$$\text{ITPC}(c, f, t) = \frac{1}{N}\sum_{n}^{N} \frac{X(c, f, t, n)}{\left|X(c, f, t, n)\right|}. \qquad (5)$$

The ITPC is phase-lock index measure the phase consistency of whole epoch. Its physiological meaning is phase consistency in difference frequency during whole epoch.

ITLC (inter trial linear coherence): The measure of phase consistency over epochs but weights epoch according to amplitude, as shown in the following:

$$\text{ITLC}(c, f, t) = \frac{1}{N}\sum_{n}^{N} \frac{X(c, f, t, n)}{\sqrt{\frac{1}{N}\sum_{n}^{N}\left|X(c, f, t, n)\right|^2}}. \qquad (6)$$

The ITLC is phase-consistency which weighted whole epoch's amplitude. Its physiological meaning is weighted phase-consistency of this ERP.

5.2.5 Statistical analysis

We used the Statistical Package for the Social Sciences (SPSS) to carry out the comparison between 2 groups in ERP averaging and Time-frequency analysis, while the alpha level of 0.0025 was used.

A specific time-frequency region was further analyzed from the post-stimulation 100 ms to 350 ms and the frequency band between 1 Hz to 5 Hz which include the most MMN waveform power. For each individual, mean value within this time-frequency region in above 6 parameters was calculated for standard and oddball stimulation. Statistic analysis was performed to compare the group difference in each parameter. To further study the relationship between the WTav, the induced activity and inter-trial phase coherence measurements in both controls and schizophrenia patients, we use the linear regression model to set WTav as a dependent variable and group effect, induced activity power and ITPC measurements as the independent variable.

5.3 Results

Demographic data of our subjects and results of traditional (grand average) ERP approach were shown in the upper part of Table 5.1. The controls showed significant younger but higher education level than the schizophrenia patients. Traditional ERP approach discovered group difference occurred in MMN mean amplitude in Fz electrode, which was compatible with previous literature.

Regarding the time-frequency results (Figure 5.1 and lower part of Table 5.1), the (two left) time-frequency plots for the standard stimuli were similar between control and schizophrenia subjects except for the avWT, which indicated the mean power from each time-frequency transformed evoke potential in each epoch. There was no significant difference in ERSP, WTav, induced activity, ITPC and ITLC of the standard stimuli between control and schizophrenia subjects.

In contrast, comparing (two right) time-frequency plots for the deviant stimuli between control and schizophrenia subjects, there is a decreased avWT (gray arrow) power in lower frequency range especially in the post-stimulation 100-350 msec in schizophrenia patients. Although there is no significant, the associated decreased coherence demonstrated by lower ITLC (blue arrow) and decreased out-phase activity power (avWT) provide the clue that schizophrenia subjects showed decreased oddball response could be explain by the desynchronized and decreased response of evoked potential. To further elaborate this issue, a regression model was use to study the relationship between the group effect, the parameters of phase-locked activity (WTav), the non-phase locked activity and inter-trial coherence (ITPC).

Using linear regression model to study the WTav in controls and schizophrenias, we found that after control the group effect, there is a significant negatively correlation with induced activity ($p < 0.0001$) and positively correlation with the ITPC ($p < 0.0001$) (Figure 5.2). The whole model p-value in both regression lines is below 0.0001 and R square is equal to 0.48 and 0.38 respectively.

5.4 Discussion

Two different approaches (averaged ERP, and time frequency analysis) were used to analyze MMN in schizophrenia patients and controls. Traditional ERP approach

discovered group difference occurred in MMN mean amplitude, which was compatible with previous literature (Michie et al., 2002; Niznikiewicz et al., 2004; de Wilde et al., 2007; Turetsky et al., 2007; Javitt et al., 2008; Keshavan et al., 2008).

The traditional signal averaging approach treats the oscillatory EEG activity as background “noise” in which the ERP “signal” is embedded, and discards the essential information(Delorme & Makeig, 2004). This missing information could be discovered using time-frequency analysis, which exhibits the underlying brain functions and their disturbances in schizophrenia patients. In our present study, we demonstrate that the group difference found in traditional approach can be further confirmed by time-frequency analysis. We also found that using the regression model approach, the measure of power in the MMN (e.g. WTav) in both group can further explain by the induced activity and coherence measurement, e.g. the higher the WTav, the lower the induced activity and higher the coherence measurement. These results could further explain that in schizophrenia subjects have lower ERP in oddball stimulation may relate to the higher induced activity and lower inter-trial phase coherence than controls.

In our current study, the demographic data showed significant age and education difference in patients and controls, which may confound our findings in current work. Besides, only the Fz channel was used in this time-frequency analysis, which may not clearly demonstrate the topographical change in the different brain regions. The whole picture of the brain activity difference in MMN could not be known. Further work should be address in the data collection and more comprehensive time-frequency analysis in whole EEG channels.

In summary, time-frequency approach explores the basic integrated neural network activity. It may also contribute to a better understanding of schizophrenia's essential pathology and the neurophysiological underpinnings in information processing.

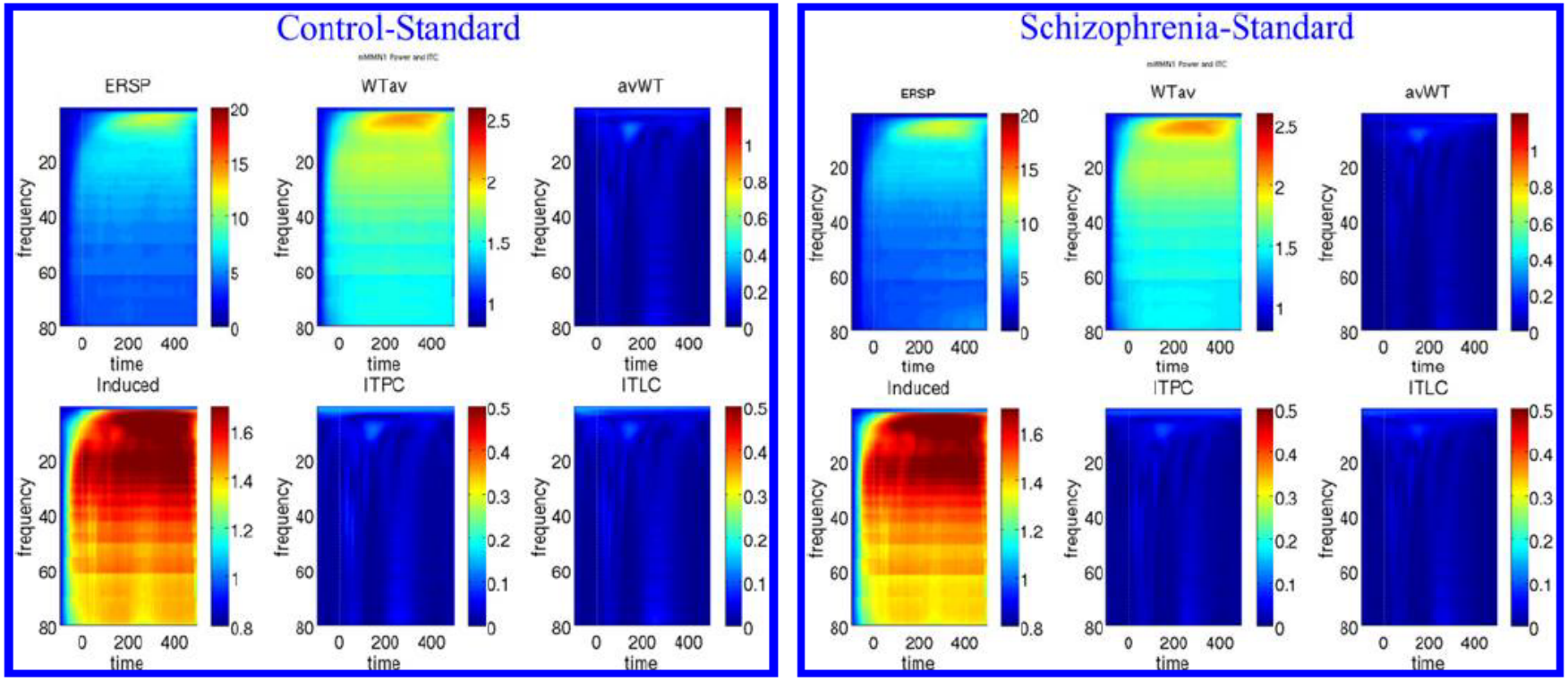
5.5 Tables and Figures

Table 5.1 Demographic Data, ERP and Time-Frequency Results in Control and Schizophrenia Subjects.

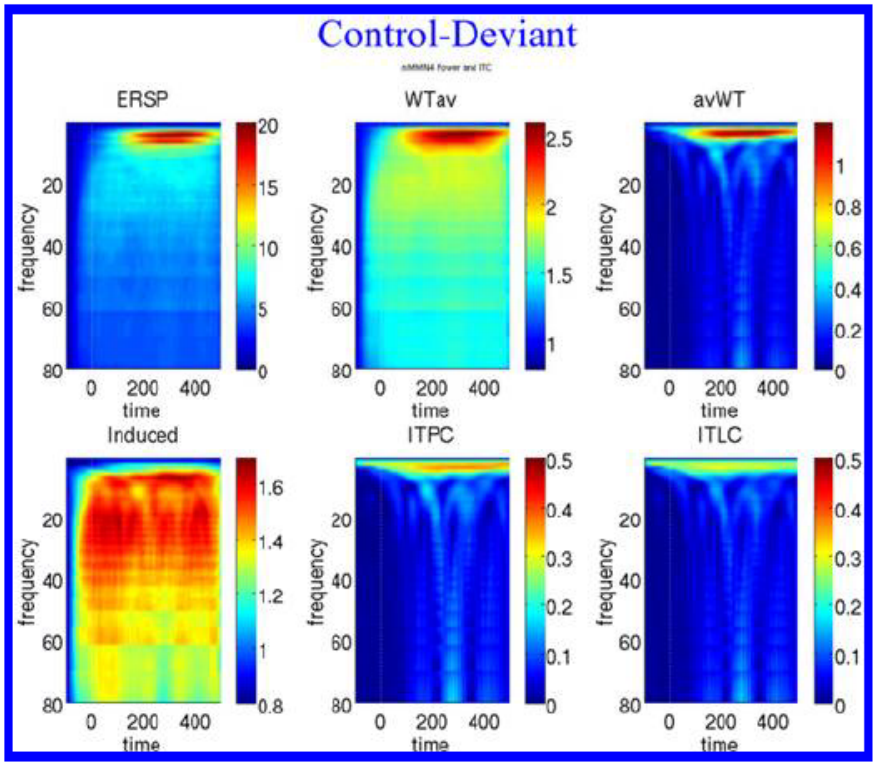
	Control ($N = 42$)	**Schizophrenia ($N = 55$)**
Male/Female	15/27	29/26
Smoking (yes/no)	2/40	10/45
	Mean ± S.D	**Mean ± S.D.**
Age (y/o)*	30.91 ± 11.11	37.98 ± 10.69
Education (years)*	15.87 ± 3.35	13.53 ± 2.58
Age of onset (y/o)	—	23.38 ± 7.32
Duration of illness (years)	—	14.60 ± 9.73
Mean amplitude approach		
Fz*	−1.12 ± 1.05	−0.5 ± 0.64
A1	0.48 ± 0.51	0.23 ± 0.52
A2	0.49 ± 0.49	0.32 ± 0.53
Time-frequency approach		
To standard stimuli		
ERSP	5.74 ± 0.66	5.65 ± 0.83
WTav (dB)	1.61 ± 0.03	1.61 ± 0.05
avWT (dB)*	−0.04 ± 0.02	−0.02 ± 0.03
Induced activity (dB)	1.42 ± 0.08	1.45 ± 0.09
ITPC	−0.03 ± 0.02	−0.02 ± 0.02
ITLC	−0.03 ± 0.01	−0.01 ± 0.02
To oddball stimuli		
ERSP	7.96 ± 4.18	6.09 ± 1.88
WTav (dB)*	1.81 ± 0.28	1.65 ± 0.08
avWT (dB)*	0.07 ± 0.06	0.04 ± 0.03
Induced activity (dB)*	1.1 ± 0.19	1.29 ± 0.14
ITPC	0.03 ± 0.03	0.02 ± 0.02
ITLC	0.03 ± 0.02	0.02 ± 0.02

*$p < 0.0025$.

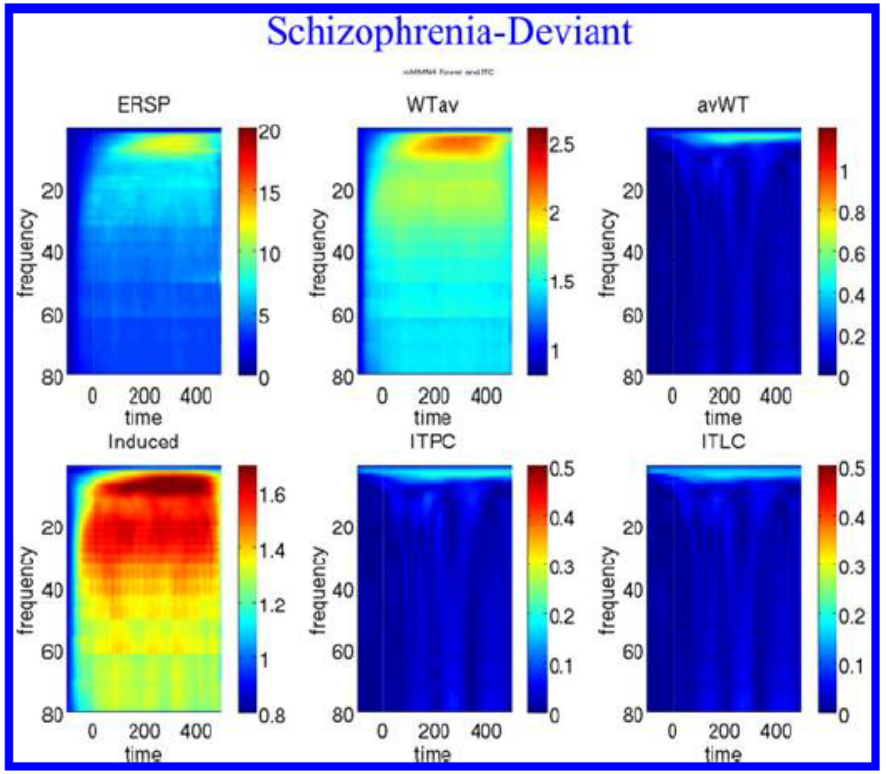
Figure 5.1 Time-frequency results of MMN. The two upper graphs show the time-frequency plots in controls, for the standard (upper left panel) and the oddball (upper right panel) stimuli. The two lower graphs reveal the time-frequency plots in schizophrenia subjects, for the standard (lower left panel) and the oddball (lower right panel) stimuli.



(A) (B)

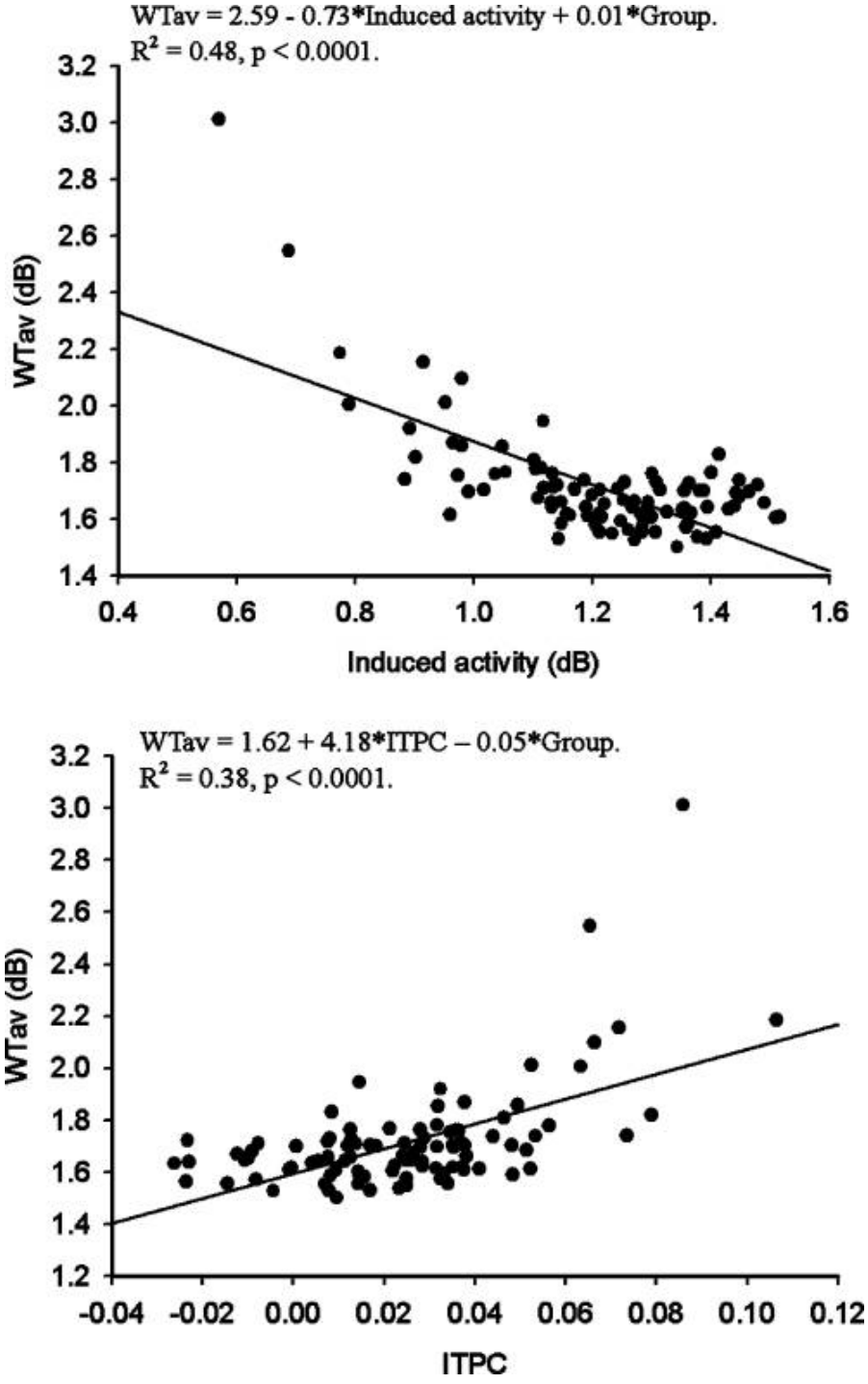

Control-Deviant
ERSP
WTav
avWT
Induced
ITPC
ITLC
frequency
time

(C)


Schizophrenia-Deviant
ERSP
WTav
avWT
Induced
ITPC
ITLC
frequency
time

(D)

Figure 5.2 Scatter plot of regression model between WTav, induced activity and ITPC within controls and schizophrenia subjects. The upper graph shows the WTav significantly negative correlation with induced activity. The lower graph reveals WTav's significantly positive correlation with ITPC.



Chapter 6. Conclusion

6.1 Summary of Current Findings of NTUH ERP-lab

Under the supervision and encouragement of Professor Hai-Gwo Hwu, Professor Ming-Jang Chiu and Professor Fu-Shan Jaw, we built up an ERP laboratory with sound-attenuating and electrically shielded booth, standard operation procedure for ERP and ERP technique real-time update. In this dissertation, we proposed 4 different views of ERP research according to the three dimensions (Disorder dimension; ERP and other measure dimension; ERP analysis method dimension) shown in Figure 1.3

1. Chapter 2 demonstrated a traditional ERP (P50) analysis method alone in schizophrenia patients vs. control subjects(Shan et al., 2010). Previous studies have placed more emphasis on S1's role in P50 sensory “gating in” and its clinical correlation (Myles-Worsley, 2002; Potter et al., 2006; Swerdlow et al., 2006; Brockhaus-Dumke et al., 2008) while our study highlights the significant role played by the S2 response (“gating out”).
2. Chapter 3 analyzed the results between MMN and neurocognition in schizophrenia patients vs. control subjects (Y. T. Lin et al., 2012). In this study, the mismatch negativity (MMN) deficit of schizophrenia was first replicated in a Han Chinese population, and then the MMN was combined with several neuropsychological measurements to differentiate schizophrenia patients from healthy subjects. The multivariate approach combining biomarkers from different modalities such as electrophysiology and neuropsychology had a better classification utility.
3. Chapter 4 compared the ERP (P50/N100/MMN) in high-risk group(suspected pre-psychotic state) vs. control subjects(Hsieh et al., 2012). Our results provide new insight regarding pre-attentional auditory ERP in subjects across different

risk levels of psychotic disorders. Impaired deviance detection shown by MMNs already exists in people at a pre-psychotic state regardless of clinical severity, while sensory gating deficits shown by P50/N100 varies depending on the risk levels in prodromal period.

4. Chapter 5 utilized time-frequency analysis for MMN in schizophrenia patients vs. control subjects (Hsu et al., 2011). Besides the traditional grand average approach, the continuous data files were also used for time-frequency analysis via ERPwavelab. In time-frequency analysis, schizophrenia subjects have lower inter trial phase coherence than controls.

6.2 Future Work

In order to popularize ERP research in medical profession, I gave talks about ERP in 台北榮民總醫院、慈濟醫院、馬偕醫院、三軍總醫院、長庚醫院、萬芳醫院、雙和醫院、新光醫院、台北市立聯合醫院松德院區、亞東醫院、國軍北投醫院etc. these years, after I entered Graduate Institute of Biomedical Engineering, NTU College of Medicine and College of Engineering. In addition, we made an educational publication in the journal台灣醫界(黃偉烈 et al., 2010). Besides, I also established an ERP-LAB website **http://erp-lab.blog.ntu.edu.tw/** to communicate with interested researchers[1]. I will keep my efforts to encourage scholar's awareness of ERP application in brain and mind science.

Future integration of ERP research network includes three different dimensions.

[1] **http://erp-lab.blog.ntu.edu.tw/** had 370,749 web views on 16/DEC/2012.

6.2.1 Disorder dimension

Besides schizophrenia and high-risk group(suspected pre-psychotic state),there are ERP publications including other neuropsyciatry disorders(Näätänen, 2003), for example

1. Neurology disorders: dementia associated with Parkinson's disease(Bronnick et al., 2010), coma(Fischer et al., 2000), traumatic brain injury (Arciniegas & Topkoff, 2004), etc.
2. Other psychiatry disorders: such as ADHD (Barry et al., 2003; Herrmann et al., 2009), autism and Asperger syndrome (Kemner et al., 2002; Jansson-Verkasalo et al., 2003; Bomba & Pang, 2004; Lepisto et al., 2006; Lepisto et al., 2007), etc.

In fact, we have recruited autism subjects for MMN and P50 under alliance with Dr. Yi-Lin Chien and Professor Shu-Fen Gao.

6.2.2 ERP and other measure dimension

(Please refer to Figure 1.1) ERP may represent essential “nodes” on common pathophysiological pathways from the genotype to the phenotype. Therefore, collaboration with other researchers to explore the relationship between ERP (measures information processing) and genes, neurocognition, functional neuroimaging, etc. is crucial in neuroscience research.

6.2.3 ERP analysis method dimension

A 30-minute ERP recording file is usually around 300MB in size. However, traditional ERP analysis only makes use of less than 5% of 300MB after ocular artifact

correction, epoching, averaging and other signal processing procedure. More than 90% information of the original file was discarded.

Novel practice ways of ERP analysis made use of more data from the original file (Figure 6.2). For example, we can employ time-frequency analysis (Morup et al., 2007; Hsu et al., 2011), ERP source localization (Fuchs et al., 2004; Michel et al., 2004), HRV calculation, etc.

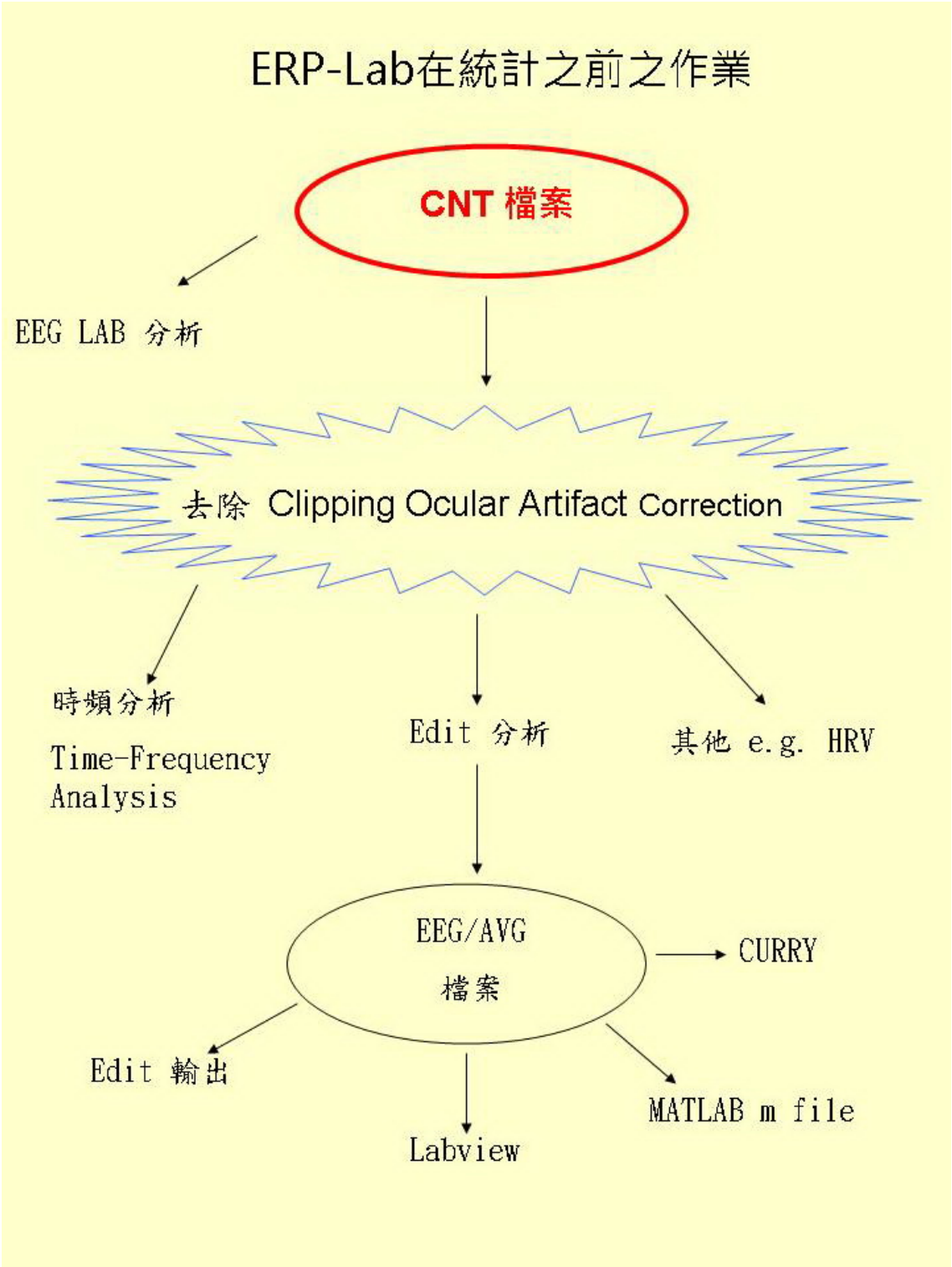
Recently, we collaborated with Professor Ming-Jang Chiu and Professor Lai's research groups in Graduate Institute of Biomedical Electronics and Bioinformatics, NTU. Using P50 and MMN continuous file, analyzing all important time fragments in a record using the probability density function of each Gaussian distribution, the proposed work can differentiate schizophrenia patients from control subjects.

By applying ERP in these three dimensions under integration with other professionals, we can elucidate the information processing details with innovative research in the future.

6.3 Tables and Figures

Figure 6.1 ERP-LAB website. http://erp-lab.blog.ntu.edu.tw/

Figure 6.2 Application of the original ERP continuous file.



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