LITERATURE REVIEW: Theta-power and phase-synchrony during memory encoding, retention and retrieval: Applications to schizophrenia

EMPIRICAL PAPER: Theta-power and memory retrieval: Applications to schizotypy

Submitted by Amie Doidge, to the University of Exeter

as a thesis for the degree of Doctor of Clinical Psychology, May 2018

I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

Signature:

Dedication

This thesis is dedicated to my grandmother, Katherine Doidge; the strongest woman I know. Thank you for instilling your determination in me. It has carried me far. You will be glad to know I have finally finished school…. For now… ☺

Acknowledgements

This process has been one of the most challenging experiences I have been through. I'm glad I had the opportunity to go through it with some wonderful people, to share the burden. There are too many wonderful people to mention everyone, but special thanks must go to Gary Lyle, Jude Fosbraey and Stuart Smith for reminding me to calm down and have fun when everything felt a bit too much.

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SCHOOL OF PSYCHOLOGY

DOCTORATE IN CLINICAL PSYCHOLOGY

LITERATURE REVIEW

Theta-power and phase-synchrony during memory encoding, retention and retrieval: Applications to schizophrenia

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Abstract

This systematic review sought to identify and synthesise available literature investigating: i) the role of theta-activity in encoding, retention and retrieval, and ii) whether people with and without schizophrenia exhibit differential theta-activity during these processes. Out of 300 papers initially identified via six databases, 24 papers were submitted for full-text review; papers were excluded based on pre-specified exclusion criteria. Of the 24 papers submitted for full-text review, seven studies were included in this final synthesis in accordance with pre-specified inclusion criteria. Of these, two papers specifically addressed encoding, five retention and two retrieval. Results for the involvement of theta to encoding and retrieval were inconsistent; there was more evidence that theta-activity was implicated in retention. Considering differential theta-activity between people with and without schizophrenia, most papers investigated retention. The principal finding was that people with schizophrenia exhibited increased theta-activity over left-lateralised scalp locations compared to control participants. There is some evidence this differential activity contributed to observed differences in memory performance. Further research is required to better understand the association between this pattern of activity and deficits in memory performance and/or functional outcomes for this population.

Introduction

Episodic memory (EM) refers to the ability to remember events and associated details, such as time, place, people or emotions. Arguably however, there are multiple processes that contribute to successful EM at different stages; namely encoding, retention and retrieval (Ranganath, Minzenberg, & Ragland, 2008). Encoding refers to the initial learning of information. Retention describes the storage or maintenance of this information over time. Retrieval is the process by which this information is accessed and used at a later time. Processes acting during encoding are critical for determining the content and accessibility of events. Several processes contribute to the integration of perceptual, conceptual and action features into a coherent concept (Ranganath et al., 2008). The number, type and extent of processes engaged during this phase have been shown to influence the efficacy of encoding processes, and the quality of information retained and available for subsequent retrieval (Atkinson & Shiffrin, 1968; Craik & Lockhart, 1972).

Successful retrieval is dependent on interactions between retrieval cues and memory traces (Schacter, Eich, & Tulving, 1978). A retrieval cue refers to any stimulus that brings a memory into consciousness or behaviour (Tulving, 1985). Interference can act on these interactions and influence the likelihood of successful retrieval. One conceptualisation of interference refers to the specificity of interactions between traces and cues. The likelihood of successfully retrieving an event is contingent not only on how strongly the cue is related to the memory trace, but also how many other traces are related to this cue and the strength of these relationships (Anderson & Neely, 1996; Levy & Anderson, 2002). Another related conceptualisation of interference refers to any intervening events

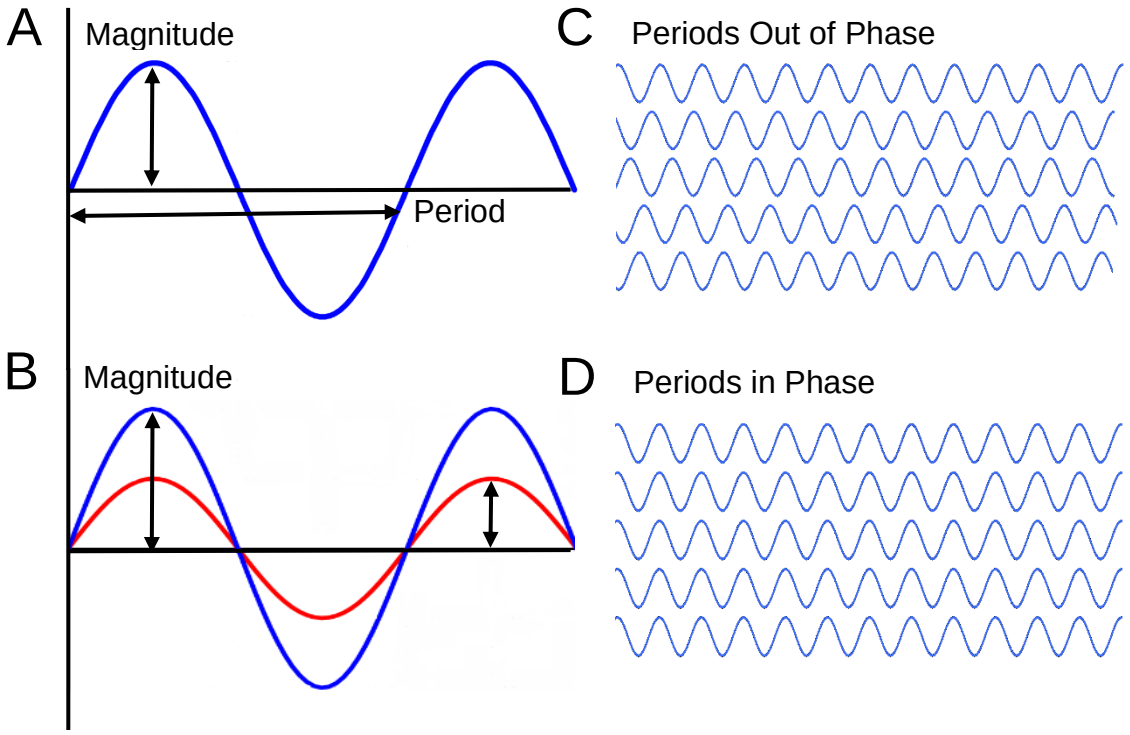

Figure 1 - Diagrams highlighting the qualities of EEG waves. A) This diagram represents a sinusoidal waveform. The magnitude refers to the maximum extent of an oscillation, as indicated by the vertical arrow. The period refers to time taken for a complete waveform cycle to pass a given point. The horizontal arrow indicates a complete waveform cycle. B) This diagram represents two sinusoidal waveforms with different magnitudes, but the same period. C) This diagram represents multiple waveforms with the same period, however the periods are not synchronous with each other. This pattern of activity can be referred to as 'out of phase'. D) This diagram represents multiple waveforms with the same period, where the periods are synchronous with each other. This pattern of activity can be referred to as 'in phase'.

occurring between the current retrieval attempt and the past, to-be-remembered event (Tomlinson, Huber, Rieth, & Davelaar, 2009). The number of events and degree of similarity between interim and to-be-remembered events influences the extent of interference (McGeoch & McDonald, 1931).

Neural activity is known to underlie cognition, including these processes associated with EM and working memory (WM). Neural activity can be characterised as event-related changes in magnitude (size) and phase (position at a point in time) at specific frequencies (see Figure 1 for a diagram of these qualities; Makeig, Debener, Onton, & Delorme, 2004). Notably, different neurons

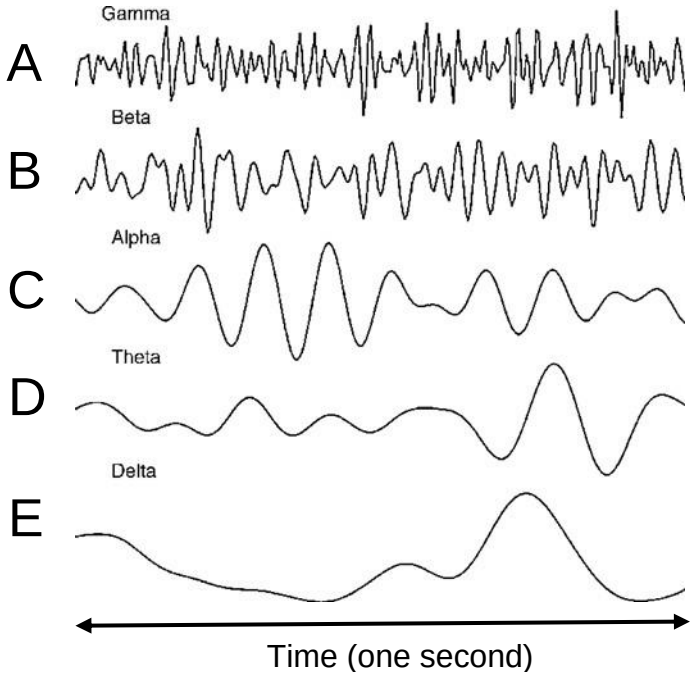

Figure 2 - A diagram showing different EEG rhythms that have been identified in human participants. The lines represent a typical pattern of activity observed for different frequencies (number of periods over a one second time window). A) Gamma (25Hz-100Hz) has generally been found to be associated with higher-order cognitive functions such as executive function and insight processes. B) Beta (12-25Hz) has been found to be associated with alert or focused mental states. C) Alpha (8-12Hz) is more commonly observed during relaxation or when eyes are closed. D) Theta (4-8Hz) is considered to be an important frequency involved in memory processing and response inhibition. E) Delta (<4Hz) is more commonly associated with sleep states.

are located in particular brain regions and have a tendency to fire at specific frequencies; different frequencies have been associated with specific cognitive functions. Brain lesion studies of rodents and humans have highlighted the principal brain areas implicated in EM and WM; neocortical and medial temporal lobe structures, specifically the hippocampus (e.g. Nyhus & Curran, 2010; Scoville & Milner, 1957; Vargha-Khadem et al., 1997; Watrous & Ekstrom, 2014; Yonelinas, 2002). Two frequencies that have been strongly associated with EM and WM are gamma (25-100Hz) and theta (4-8Hz; e.g. Nyhus & Curran, 2010; Watrous & Ekstrom, 2014; refer to Figure 2 for more information about neural frequencies).

Nyhus and Curran (2010) conducted a review and identified that during encoding, gamma phase-synchrony increased and theta-power (magnitude squared) increased for items that were successfully recalled compared to those that were subsequently forgotten. Furthermore, they identified that during successful retrieval gamma- and theta-power increase over posterior scalp locations. Theta was also found to modulate gamma-activity over anterior scalp locations. In view of this, they proposed that gamma- and theta-activity transiently interact within cortico-hippocampal circuits to facilitate the encoding and retrieval of episodic events. Specifically, gamma-activity acts to bind perceptual and contextual features into episodic representations, and theta-activity acts to temporally order these representations in the hippocampus. Neural feedback in cortico-hippocampal circuits then serves to reinstate these representations during retrieval. Furthermore, theta-activity may facilitate top-down control of representations during encoding and retrieval (Nyhus & Curran, 2010). Whilst there is little debate about the importance of contextual overlap between encoding and retrieval; how such contexts are reinstated in the brain is poorly understood (Watrous & Ekstrom, 2014).

The spectro-contextual encoding and retrieval theory (SCERT; Watrous & Ekstrom, 2014; see Figure 3 for a representation of this model) proposes there is rhythmicity in the external world; for example natural sounds and speech (Singh & Theunissen, 2003). For signals from arrhythmic stimuli, rhythmicity can be imposed through sensory sampling via motor actions within the environment, a process known as active sensing (Schroeder, Wilson, Radman, Scharfman, & Lakatos, 2010) These rhythmic inputs act as frequency- and phase-specific internal contexts during encoding and can cause synapses to fire. Synaptic firing

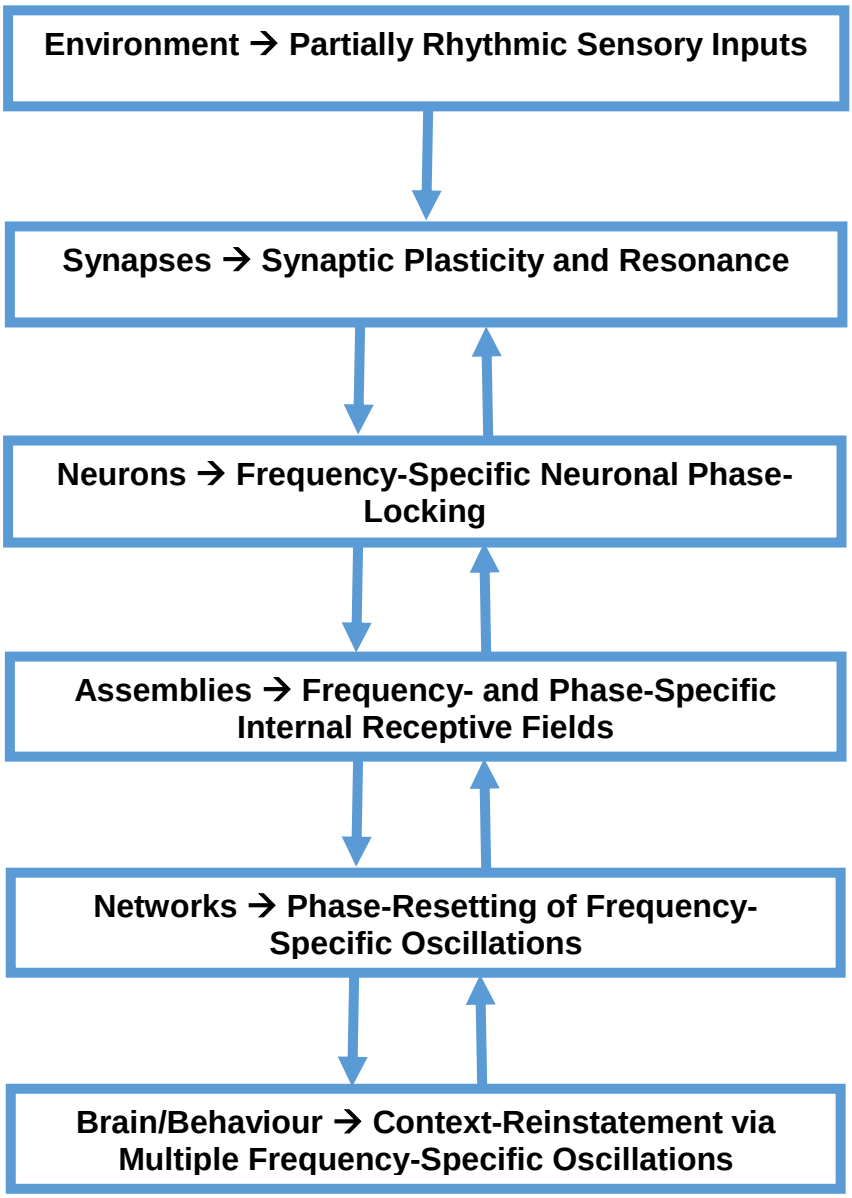

Figure 3 - Schematic representation of the levels of neural organisation within the brain and the principal findings that contributed to the development of SCERT (Watrous & Ekstrom, 2014). Figure reproduced from Watrous and Ekstrom (2014).

promotes activity in other neurons responsive to similar properties, thus contributing to the formation of functional cell assemblies (Narayanan & Johnston, 2007). Patterns of activity across cell assemblies, such as cross-frequency coupling and phase-synchrony, are strengthened or weakened via Hebbian plasticity; thus contributing to the encoding of environmental signals (Axmacher, Mormann, Fernández, Elger, & Fell, 2006; Canolty & Knight, 2010;

Hebb, 1949). Sustained activity across these networks contributes to the retention of these encoded signals; processes highly implicated in EM and WM tasks (Jensen & Lisman, 1998; Ranganath, Cohen, & Brozinsky, 2005). Reactivation of cell assemblies during retrieval are hippocampus-driven; internal or external contextual cues promote activity across cell assemblies primed, through the process of encoding, to those inputs (Canolty & Knight, 2010; Nadel & Moscovitch, 1997). Importantly, reactivation of cell assemblies is multiplexed, meaning that multiple signals can be communicated through a single communication channel (Akam & Kullmann, 2014); permitting accounts of interference in EM.

Several behavioural WM and EM paradigms have been developed to examine processes contributing to different stages of memory. Both WM and EM memory tasks are able to provide overall behavioural measures of memory retrieval, namely probability of correct responses to items (accuracy), and reaction times (RTs). Certain WM and EM tasks however, in conjunction with neuroimaging methods, are able to provide insights into encoding and retention stages of memory processing as well; particularly when time-sensitive methods such as EEG are used. The following sections will briefly introduce common paradigms used to investigate WM and EM and what measures of behavioural performance can be derived.

Two of the most commonly used WM tasks are n-back (Kirchner, 1958) and oddball tasks (Squires, Squires, & Hillyard, 1975). During n-back tasks, participants are presented with a sequence of stimuli. Participants are required to indicate if the current stimulus matches the n^{th}-previous item in the sequence (Kirchner, 1958). During oddball tasks, participants are presented with a series of

repetitive stimuli infrequently interrupted by deviant stimuli (Squires et al., 1975). Participants are usually required to make a response to deviant stimuli. Considering successful WM performance for both tasks involves the interaction of multiple cognitive processes, it is difficult to differentiate whether poor performance can be attributed to deficits in one or all of these processes, due to the cascade effect of altered processing, or indeed the integration of these processes (Lesh, Niendam, Minzenberg, & Carter, 2011). Consequently, other WM paradigms have been developed that permit differential measures of behavioural performance for encoding, retention and retrieval processes when used in conjunction with neuroimaging methods.

The Sternberg Item Recognition Paradigm (SIRP; Sternberg, 1969) involves presenting participants with a list of items to study. Participants are required to maintain this list in memory for a short period of time. Subsequently, participants are presented with a probe item and required to indicate if this item was in the initial studied list. Similarly, in the delayed-match-to-sample paradigm (DMTS; Skinner, 1950), participants are presented with a sample item. Following a retention period, participants are presented with a set of stimuli and asked to indicate which one matches the sample. In addition to providing behavioural measures of memory retrieval as previously highlighted, given the distinct encoding, retention and retrieval phases of these tasks, when used in conjunction with neuroimaging methods, it is possible to investigate processes specific to these phases.

The principle EM task that are used are recognition paradigms. Recognition memory paradigms involve presenting participants with a series of items to study. Frequently, participants are required to make judgments on these

items to facilitate encoding (e.g. would the items fit in a shoe box, yes or no; Evans, Wilding, Hibbs, & Herron, 2010). These items are subsequently re-presented during a test phase intermixed with new (unstudied) items.

In relation to EM paradigms, typically those designed to investigate encoding are different to those designed to investigate retrieval. This is due to the competing requirements of analysis strategies for behavioural performance and neuroimaging measures. A certain level of behavioural performance has to be achieved to ensure participants are able to do the task, and any outcomes cannot be attributed to floor effects. This has to be balanced against the requirements for neuroimaging analysis which necessitate a minimum number of trials per condition of interest to have confidence that the patterns of activity obtained accurately reflect the process under investigation (Luck, 2005).

When examining encoding processes, the most common contrast is between patterns of brain activity obtained for items at encoding that were subsequently remembered compared to those that were forgotten (subsequent memory effects; Paller, Kutas, & Mayes, 1987; Paller & Wagner, 2002). Such contrasts help elucidate processes crucial to subsequent accurate memory judgments (Bridger & Wilding, 2010; Sprondel, Kipp, & Mecklinger, 2011). Consequently, whilst behavioural performance may be within reasonable limits it may not be possible to examine patterns of neural activity at both encoding and retrieval within the same paradigm. This is due to the poorer memory performance required to achieve subsequent memory effects, that may limit the number of trials available to investigate processes associated with successful retrieval.

Extensive EEG investigations have been conducted employing these tasks and event-related potential analysis methods. This approach assumes that the signal of interest is time-locked to the stimulus and is superimposed over background “noise”. Through averaging it is possible to enhance the signal-to-noise ratio (Pfurtscheller & Lopes da Silva, 1999). However, as highlighted previously it is increasingly accepted that EEG signals can be characterised as frequency-specific activity, rather than “noise”. By considering separate frequencies, specifically theta- and gamma-frequencies it may be possible to gain greater insight into the mechanisms that support multiple cognitive processes, including those adversely affected in people with schizophrenia (Roach & Mathalon, 2008).

It is widely acknowledged that the vast majority of people with schizophrenia experience cognitive deficits (Green, 1996; Green, Kern, Braff, & Mintz, 2000; Reichenberg et al., 2006). These cognitive deficits have been shown to affect a broad range of functional outcomes including, adherence to medication and psychological therapies (Burton, 2005; Prouteau et al., 2005), daily living and social skills (Bowie & Harvey, 2005) and symptom relapse (Chen et al., 2005). Whilst many cognitive domains are affected, meta-analyses have identified EM as one of the most profoundly affected (Aleman, Hijman, de Haan, & Kahn, 1999; Heinrichs & Zakzanis, 1998; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). Importantly, this domain has been identified as one of the principal predictors of functional outcome (Green et al., 2000; Nuechterlein et al., 2011; Puig et al., 2008). Together, this highlights alleviating cognitive deficits, particularly those impacting EM, as an important treatment target for people with schizophrenia.

Whilst increasingly we are understanding the processes underlying successful EM in control participants, less is known about how these processes may operate in people with schizophrenia. WM paradigms are more frequently used than EM paradigms to investigate frequency-specific activity and their role in memory performance with people with schizophrenia. A review of recent WM studies highlighted that auditory oddball tasks are most frequently used, (Basar & Guntekin, 2013). The consistent findings identified across a range of WM tasks was that people with schizophrenia, compared to control participants, exhibited reduced theta-activity, namely power and phase-synchrony during task performance (Basar & Guntekin, 2013). The relevance of these findings to behavioural memory performance was not comprehensively discussed by these authors however. One paper included in this review identified that theta-band activity was associated with the number of correct responses encoded by control participants; no such associations were identified for people with schizophrenia (Haenschel et al., 2009). No consistent findings were identified in relation to gamma-activity and differences between those with and without schizophrenia during WM tasks; differential gamma-activity was more commonly identified in visual steady-state tasks (Basar & Guntekin, 2013).

There are limitations associated with the findings of the above review. First, Basar and Guntekin (2013) highlighted that the studies reviewed recruited several subgroups of people with schizophrenia including first-episode and chronic presentations, those who were and were not taking medication. Comparing results from such diverse samples complicated synthesising findings across studies. For example, it has been well established that psychotropic medications have differential effects on EEG signals, depending on the type of

medication received (Hyun, Baik, & Kang, 2011). Consequently, the authors advocated future research should focus on minimising variability in participants to avoid these confounds. Second, as discussed previously, the WM tasks employed by the studies reviewed did not permit process-differentiation; limiting the strength of conclusions that can be drawn about the role of theta-activity to the separable processes that contribute to WM performance (Basar & Guntekin, 2013). Future research would benefit from employing tasks that can address these questions.

The literature discussed suggests theta-activity is most consistently implicated in memory processing for people with schizophrenia and control participants. Thus, the role of theta-activity to memory processing will be the focus of this review. Assertions about the relevance of this frequency band for a broad range of memory processes (e.g. encoding, retention, retrieval) for people with schizophrenia are derived from WM tasks, rather than EM paradigms. This is potentially problematic as tasks assessing WM involve the integration of multiple cognitive processes, and tasks do not always permit differentiation of these processes. Thus, it is still important to conduct investigations using paradigms specifically designed to evaluate the role of frequency-specific activity to particular processes that contribute to WM and EM. As a first step to addressing this, the present review intends to answer the following:

i) *"What is the current evidence from EM and WM paradigms that theta-activity contributes to encoding, retention and retrieval processes specifically?"*

ii) *"Do measures of theta-activity differ between people with schizophrenia and control participants?"*

Methods

Eligibility Criteria

In accordance with the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines, Participant, Exposure, Comparator, Outcome and Study Design (PECOS; Moher, Liberati, Tetzlaff, & Altman, 2009; Moher et al., 2015) criteria were used to identify studies to be included or excluded from this systematic review (details in Table 1). Principally, this highlights that studies collecting EEG/Magnetoencephalography (MEG) and behavioural data from visual-, numerical- or verbal-memory tasks for adult, human participants were considered. Although patterns of data obtained from EEG/MEG techniques are not directly comparable as EEG is sensitive to both radial and tangential sources, whereas MEG is sensitive only to tangential sources (Hauk, 2013), both methods were included to maximise findings. Data from EM and WM tasks were included, but only where measures permitted examination of the different processes that contributed to performance (e.g. separate outcomes for encoding/retention/retrieval of information). Only studies recruiting adult participants were included, except where studies explicitly investigated early-onset psychosis in adolescents (13-18 years), considering children rarely receive a diagnosis of schizophrenia. Studies using continuous measures of schizophrenia symptomatology were also included. Where patient participants were recruited, studies were only included where data were collected from relevant matched-control participants.

Table 1 - Inclusion and exclusion criteria for the systematic review

Inclusion	Exclusion

Participants	i) Human, adult participants (18+, unless explicitly examining early onset psychosis). ii) Patients diagnosed with schizophrenia/schizoaffective disorder. iii) If not a patient study, psychometric measures of schizotypy have been collected.	i) Co-morbid alcohol/substance use/dependence. ii) History of clinically significant neurological condition (e.g. stroke, brain injury, dementia). iii) Studies recruiting child participants (<13years).
Exposure	i) Schizophrenia symptomatology or schizotypy measured using diagnostic interview schedules or psychometric methods.	i) N/A
Comparator	i) Appropriately matched control group (e.g. age, gender) for patient studies and where psychometric measures of schizotypy have been dichotomized. ii) Verbal, numerical or visual EM (recognition memory paradigms) or WM tasks collected in a single testing session, where dissociable measures of encoding, retention or retrieval are available (SIRP, DMTS).	i) Insufficient EEG trials per condition of interest (<15). ii) Non-dissociable measures of encoding, retention or retrieval (e.g. oddball, n-back tasks).
Outcome	i) EEG/Magnetoencephalography (MEG) measures of oscillatory activity collected during a memory task (e.g. power and phase-synchrony). ii) Behavioural measures of memory performance at encoding and/or retrieval.	i) EEG/MEG measures collected during resting state/steady state/sleep. ii) EEG/MEG data acquired from electrode/SQUID montages with insufficient whole-head coverage (<25 electrodes). iii) EEG data acquired with insufficient bandwidth (at least 0.1-40Hz). iv) Poor behavioural performance (discrimination performance between old and new items <0.1).
Study Design	i) Case-control studies. ii) Correlational designs where psychometric measures of schizotypy have been collected.	i) Qualitative studies.

Search Strategy

Six electronic databases were searched: Medline, PsycARTICLES, Embase, Web of Science, SCOPUS and PsycINFO. The search terms below (Table 2) were used to identify and screen articles for inclusion on the basis of titles, abstracts and key terms. Truncations were used to identify all possible relevant derivatives of stem-words. Boolean “and” operators were used between,

and “or” operators were used within construct terms (see Table 2). After compiling a list of search records, these were pooled across databases; duplicate publications were deleted. Titles and abstracts for these records were then screened using the exclusion criteria (Table 1). Those that passed this stage were then screened on the basis of the full-text, and evaluated for quality. Articles were only subjected to full-text screening if they were printed in English (to avoid translation fees). Reference lists of all studies included were manually searched to identify potential additional papers. Any additional papers were also screened for inclusion using the same method described above.

An independent researcher screened 30 studies identified from the database search, and for all those included for full-text review. Considering studies investigating memory problems in people with schizophrenia are usually cohort designs, the Newcastle-Ottawa Scale for non-randomised studies was used to assess the study quality (NOS; Wells et al., 2000). This measure uses a star system to rate studies against three broad criteria: selection and comparability of group members, and the outcome of interest, and has been found to be an efficient yet comprehensive means of assessing study quality (Deeks et al., 2003). This measure was used to weight the evidence of studies in the synthesis. The study quality was also verified by an independent reviewer who assessed three of the final papers included in the systematic review.

Table 2 - List of search terms used to identify papers for the systematic review

Construct	Search Terms

Schizophrenia	schizo* OR psycho* AND human
Memory	explicit OR episodic OR recognition OR recall OR recollection OR working OR memory OR encoding OR learning OR retention OR maintenance OR retrieval
Neural Oscillations	frequency OR oscillat* OR evoked OR induced OR synchron* OR power OR phase OR coherence
Measure of Brain Activity	electroencephalo* OR EEG OR magnetoencephalo* OR MEG
Frequency	theta

Results

A total of 313 records were identified (300 when duplicates were removed). Screening using PECOS criteria resulted in 24 records that were submitted to full-text review. Following full-text review, a further 16 records were excluded due to: i) task design being unable to differentiate processes (10), ii) electrode montages with insufficient head coverage (3) and, iii) no memory paradigm being used (3). Reviewing the reference lists from all records submitted for full-text review identified a further four papers; however none were included based on the following reasons: i) data were not collected from people with schizophrenia (1), ii) no memory paradigm was used (3). Consequently, a total of seven records were included in this systematic review and rated for study quality using NOS (Wells et al., 2000). Inter-rater reliability highlighted 100% concordance at all stages (initial screening, full-text review and study quality).

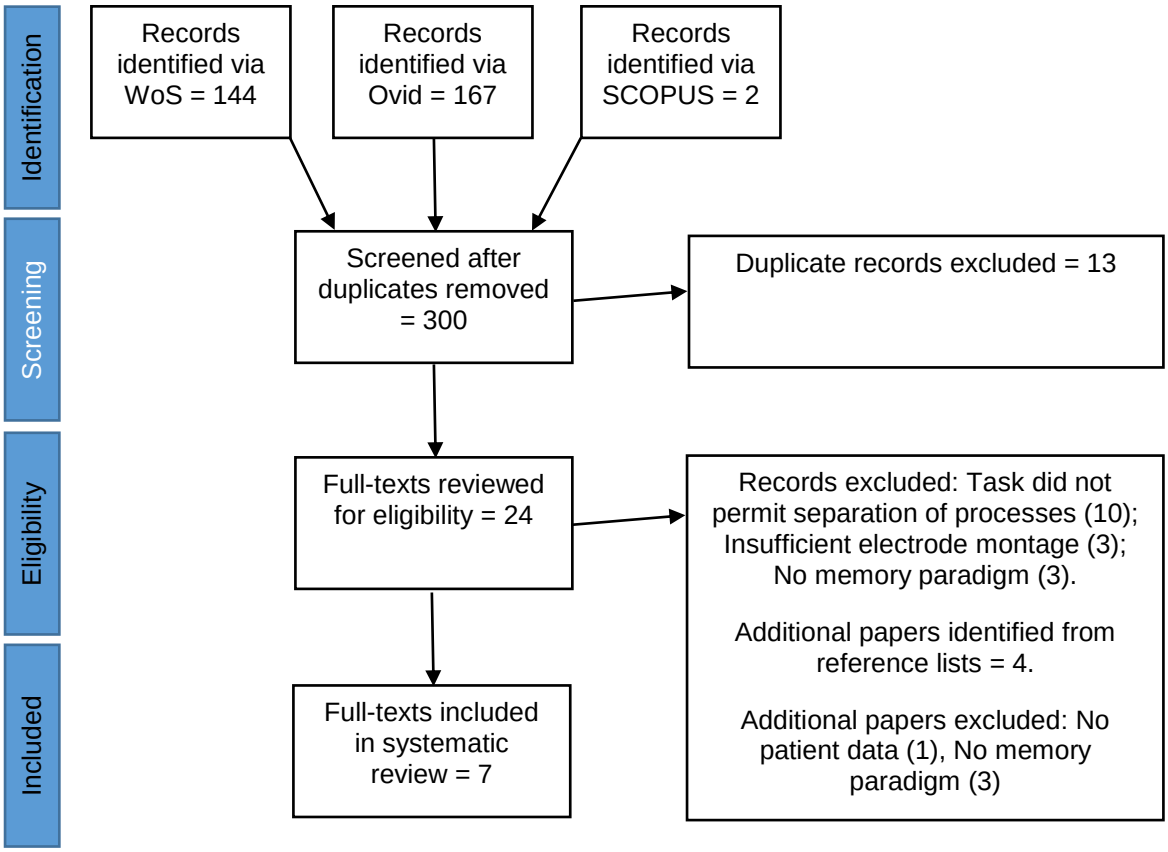

Figure 4 – A flow chart detailing the number of studies identified and included/excluded at each stage of the protocol. WoS = Web of Science (1900-February 12, 2018); Ovid = Embase (1974-February 12, 2018), Ovid Medline ®In Process and Other Non-Indexed Citations (1946-February 12, 2018), PsycINFO (1806-February 12, 2018), PsycARTICLES; SCOPUS = (-February 12, 2018)

Critical Summary

Overview

Of the seven studies included, five studies collected data from people with schizophrenia (1, 2, 3, 5, 6); one of these studies collected data from people with early-onset schizophrenia (6). Two collected data from student populations (4, 7).

Of the five studies collecting data from people with schizophrenia, two studies determined diagnostic status by recruiting via hospitals/clinics (1, 5); two via Diagnostic Statistical Manual of Mental Disorders (DSM-IV; APA, 1994) interview schedules (2, 6); and one via two independent psychiatric reviews (3). The two studies using student samples collected measures of schizotypy using

versions of the schizotypal personality questionnaire (4, 7; Raine, 1991), a valid and commonly used measure.

All studies matched participants in terms of age and gender. Additionally, three studies (3, 6, 7) matched participants on their pre-morbid IQ, as measured by variants of the National Adult Reading Test (Nelson, 1982). Similarly, (4) matched participants on years in education. Four studies collected behavioural data using DMTS (2, 5, 6, 7); two used SIRP (1, 3) and one used a continuous recognition paradigm (4). A wide range of stimuli were used across these tasks.

Two studies examined theta-activity in relation to encoding (6, 7; refer to Table 3 for the key features of each study); six in relation to retention (1, 2, 3, 5, 6, 7) and three in relation to retrieval (4, 6, 7). Six studies measured theta-activity using EEG (1, 2, 4, 5, 6, 7), one used MEG (3). A wide range of metrics were used to investigate theta-activity. Some papers included analyses of other measures or groups beyond those being investigated in this review. Only findings relevant to the present research questions are discussed here (see *Table 4* for a critical summary of the included studies).

Table 3 – Descriptive summary of studies included in this systematic review. Studies are listed in alphabetical order by author. The number that corresponds to the study will be used to refer to the study in subsequent tables and passages.

Author	Exposure and How Determined	Behavioural Task and Stimuli Used	Neural Measure	Stage?	Theta Involved	Between Group Difference
1. Baenninger, Hernandez, Rieger, Ford, Kottlow & Koenig (2016)	Schizophrenia; Recruited from hospital/clinic	SIRP; Letters	Simultaneous EEG-fMRI; covariance of theta during retention with pre-encoding fMRI activity.	Retention	Yes	Yes
2. Brenner, Rumak & Burns (2016)	Schizophrenia and schizoaffective disorder; Structured	DMTS; Facial expressions	EEG; theta-power; correlations between theta-power and	Retention	Yes	Yes

	Clinical Interview for DSM-IV		behavioural performance			
3. Canuet et al (2010)	Schizophrenia; Determined by two independent psychiatric reviews.	SIRP; Numbers	MEG; power changes in theta, event-related synchronisation (increase in power relative to baseline) and de-synchronisation (decrease in power relative to baseline).	Retention	Yes	Yes
4. Choi, Jang, Jung, Kim & Kim (2016)	Schizotypy; Korean version of the Schizotypal Personality Questionnaire (SPQ).	Continuous recognition paradigm; Words	EEG; event-related spectral perturbation, induced (non-phase-locked) theta-band activity (TBA), theta phase-locking value (PLV; measure of phase-synchrony).	Retrieval	Yes	No – not identified in higher order analyses; only in post-hoc pairwise compariso ns
5. Griesmayr, Berger, Stelzig-Schoeler, Aichhorn, Bergmann & Sauseng (2014)	Schizophrenia; Recruited from inpatient and outpatient hospital/clinic	DMTS; Visuo-spatial (coloured blocks)	EEG; event-related magnitude, theta phase-locking values (PLV).	Retention	Yes	Yes
6. Haenschel et al (2009)	Early-onset schizophrenia; DSM-IV criteria, Positive and Negative Symptom Scale (PANSS)	DMTS; Blurred outlines of random Tetris shapes (BORTS)	EEG; grand mean induced and evoked oscillatory theta.	i) Encoding ii) Retention iii) Retrieval	i) Yes ii) No iii) Yes	i) Yes ii) N/A iii) Yes
7. Koychev, Deakin, Haenschel & El-Deredy (2011)	Schizotypy; SPQ	DMTS; BORTS	EEG; phase-locking factor (PLV), signal power.	i) Encoding ii) Retention iii) Retrieval	i) No ii) No iii) No	i) No ii) No iii) No

Encoding

Both of these studies (6, 7) collected EEG data whilst participants completed a visual-DMTS. (6) collected data from people with early onset

schizophrenia and matched control participants, and (7) adopted an endophenotypic approach and collected data from those high and low in schizotypy. Importantly, both samples limit the impact of patient factors (e.g. duration of illness, medication) that often confound research using patient participants.

Behaviourally, both studies identified RTs increased for higher WM loads for both groups of participants. Similarly, those high in schizotypy were found to be less accurate compared to those low in schizotypy (7), and people with schizophrenia were found to successfully encode fewer items compared to control participants (6).

No significant effects were identified between those high and low in schizotypy in relation to theta-power (magnitude squared) or theta phase-locking factor (PLV; a measure of phase-synchrony; 7). A significant effect of WM load was identified, and post-hoc comparisons revealed differences between groups in relation to this. However, as differences at the level of higher-order analyses were not identified, this outcome should be considered with caution. By contrast, (6) found that people with schizophrenia exhibited significantly reduced evoked-theta-activity (phase-locked to stimulus-onset) compared to control participants during the encoding phase. Evoked-theta was more prevalent over anterior than posterior electrode locations. Furthermore, anterior evoked-theta-activity was found to correlate with the number of items successfully encoded for control participants, but not for people with schizophrenia. Based on this, (6) advocated that behavioural performance is predicted by evoked-theta during encoding, but this association is disrupted for people with schizophrenia.

In relation to the NOS (Wells et al., 2000), both studies only achieved four stars out of a possible nine. Whilst both studies seemed to match their groups well, there was limited information available about recruitment; limiting the extent to which these samples can be considered representative of their respective target populations. Taking this into consideration, the above findings should be considered with caution.

Retention

Six papers examined theta-activity in relation to retention processes (1, 2, 3, 5, 6, 7). Of these papers, four indicated theta-activity contributed to these processes (1, 2, 3, 5), and that theta-activity differed between groups of participants. These four studies recruited people with schizophrenia. The remaining two studies (6, 7) did not find evidence for the involvement of theta to retention processes. Of these studies, one recruited people with early onset schizophrenia (6), the other recruited student participants and collected measures of schizotypy (7). All studies collected EEG data, with the exception of one (3) where MEG data was collected.

Four studies used DMTS, though employed different stimuli (2, 5, 6, 7; facial expressions, coloured blocks, blurred outlines of random Tetris shapes [BORTS], and BORTS respectively). The remaining two studies used SIRP, and similarly employed different stimuli (1, 3; letters and numbers respectively). Across studies, the consistent finding seemed to be that people with schizophrenia or those scoring high in schizotypy performed less accurately than control participants (1, 2, 5, 6, 7). (1) also found people with schizophrenia had slower RTs compared to control participants. Only one study (3) found no

differences in behavioural performance between groups. It is noted however, that this study was not designed specifically to examine differences between people with schizophrenia and control participants. Rather, this study was designed to compare those with chronic interictal psychosis to people with schizophrenia.

Table 4 – Critical summary of studies included in this systematic review.

Author	Exposure	Comparator	Results and Conclusion	Strengths and Limitations	Newcastle-Ottawa Scale (Case Control)
Encoding					
6.	14 PwEOS (9 males, 5 females; mean age: 17.76 ± SD: 1.44 years; premorbid IQ: 97 ± SD: 14).	14 control participants (7 males, 7 females; mean age: 17.37 ± SD: 1.41 years; premorbid IQ: 95 ± SD: 8).	Behaviour: Number of successfully encoded items was lower for patient compared to control participants. EEG: PwS showed significantly reduced evoked theta-activity compared to control participants. Evoked anterior theta-activity predicted the number of items encoded for control, but not for patient participants. Conclusions: Results suggest that WM deficits in PwS are associated with impaired oscillatory activity, including theta, during encoding.	Strengths: i) Examined encoding retention and retrieval in the same paradigm. ii) First episode patient participants were recruited for this study, therefore reducing the impact of medication and duration of illness effects. Limitations: i) Small samples for between group comparisons. ii) Unclear whether analyses have been corrected for multiple comparisons.	Selection i) One Star ii) No Star iii) No Star iv) No Star Comparability i) Two Stars Exposure i) One Star ii) No Star iii) No Star **Total: 4/9**
7.	18 high schizotypes (12 male, 6 female; mean age: 23.1 ± SD: 4.1 years; premorbid IQ: 114.3 ± SD: 4.8 as determined by the NART).	20 low schizotypes (13 male, 7 female; mean age: 23.5 ± SD: 3.4 years; premorbid IQ: 114.9 ± SD: 4.8 as determined by the NART)	Behaviour: No RT differences between groups. High SPQ group had significantly lower accuracy compared to low SPQ group. EEG: No significant effects of schizotypy were found. Conclusion: Most significant effects obtained were in relation to beta and gamma, rather than theta. Limited evidence for the role of theta to WM performance obtained here.	Strengths: i) Endophenotypic approach limits impact of patient factors (e.g. medication, length of illness) that typically confound patient research. ii) Examined encoding, retention and retrieval in the same paradigm. Limitations: i) Limited information about recruitment and the representativeness of group status. ii) Group differences identified through post-hoc pairwise	Selection i) No Star ii) No Star iii) No Star iv) One Star Comparability i) Two Stars Exposure i) No Star ii) One Star iii) No Star **Total: 4/9**

				comparisons rather than higher order analysis.	
Retention					
1.	17 PwS(14 male, 3 female; mean age: 34.62 ± SD: 8.79 years)	17 control participants (14 male, 3 female; mean age 31.62 ± SD: 7.06 years)	Behaviour: Compared to control participants, PwS responded more slowly and less accurately, especially at higher WM loads. EEG: Coupling between the default mode network (DMN) and theta during retention, and the dorsal attention network (DAN) and theta during retention was significantly different between PwS and control participants. Conclusion: For PwS the relationship between pre-encoding activation and EEG activity during a retention period are altered, which contributes to deficits in WM.	Strengths: i) TANCOVAs of these measures with medication, severity of symptoms and cognitive performance revealed no significant effects. ii) Effects relating to fronto-medial theta and DMN were analysed for an earlier time window, than previous literature indicated. However, reanalysis of previous data also identified effects in this time period. Limitations: i) Data analysis was restricted by lack of consistent covariance maps and load effects across groups.	Selection i) One Star ii) One Star iii) One Star iv) One Star Comparability i) Two Stars Exposure i) No Star ii) No Star iii) No Star **Total: 6/9**
2.	38 PwS (27) or schizoaffective disorder (11; 15 male, 23 female; mean age: 31 ± SD: 8.65 years)	42 control participants (16 male, 25 female; mean age: 31 ± SD: 8.51 years). NB: Noted number of reported males and females do not add to the 42 participants reported.	Behaviour: Control participants were significantly more accurate than PwS. EEG: Analysis of theta-power over left-frontal locations revealed greater power for PwS compared to control participants. Inverse correlation between theta-power and behavioural performance for controls. Conclusion: PwS exhibited greater theta-power during the retention period, compared to control participants, suggesting PwS devote excessive cognitive resources to the maintenance of emotional information.	Strengths: i) Good sample size for between subjects contrast. Limitations: i) No passive viewing control condition. Effects of motor responding cannot be differentiated. However, this would not explain differences between emotions. ii) Low trial numbers (only 20 trials/emotion, even if 100% accuracy and no artifacts in EEG data). Does not report minimum number of trials required to include participant.	Selection i) One Star ii) No Stars iii) No Star iv) One Star Comparability i) Two Stars Exposure i) No Star ii) No Star iii) No Star **Total: 4/9**

3.	14 PwS (9 male, 5 female; mean age: 34.9 ± SD: 10.2 years, premorbid IQ: 100.6 ± SD: 9.4 as measured by the Japanese Adult Reading Test [JART]).	14 control participants (9 male, 5 female; mean age: 34.2 ± SD: 11.3 years, premorbid IQ: 101.2 ± SD: 24.8 as measured by the JART).	Behaviour: Box plots and discussion suggest there is no significant difference between control participants and PwS in terms of accuracy or RT (significant overlap of IQR). MEG: Significant difference in theta-power changes between PwS and control participants over left inferior temporal cortex. Most significant differences identified in relation to alpha however. Conclusion: Changes in alpha power during the retention period over right DLPFC and left temporal cortex are more commonly observed in this task, compared to changes in theta.	Strengths: i) Controls are well-matched to patient participants. ii) Button press for recognise and do not recognise probe. This means that differences in activity are unlikely to be due to motor responding. Limitations: i) Study designed to investigate similarities/differences between PwS and chronic interictal psychosis, a third group not relevant to the current research question. ii) Small sample size. iii) Low trial numbers contributing to average patterns of activity (only 20 trials maximum, minimum trial number =15).	Selection i) One Star ii) One Star iii) One Star iv) One Star Comparability i) Two Stars Exposure i) One Star ii) No Star iii) No Star **Total: 7/9**
5.	20 PwS (16 male, 5 female; mean age: 31.96, range: 22–46.02 years). NB: Paper reports 21 patients and controls however, behavioural and EEG results only report data from 20	19 control participants (16 male, 5 female; mean age: 31.55, range: 20.05–47.02 years).	Behaviour: PwS performed significantly worse in the manipulation condition at higher WM loads compared to control participants. EEG: Control participants but not PwS exhibited a load dependent increase in theta magnitude over posterior locations. The percentage of correct responses in the manipulation condition was significantly correlated with the PLV ratio for the manipulation and retention condition indicating higher performance when patterns of activity were more similar to those for control compared to patient participants. Conclusion: Pure retention seems to be intact in patients with	Strengths: i) No consistent effects identified when CPZE equivalents entered as a factor suggesting that medication effects are not consistently influencing the findings. Limitations: i) Not all analyses were corrected for multiple comparisons. The results would be unlikely to withstand correction for multiple comparisons given the small sample size and the number of comparisons conducted.	Selection i) One Star ii) No Star iii) No Star iv) One Star Comparability i) Two Stars Exposure i) One Star ii) No Star iii) No Star **Total: 5/9**

	patients and 19 controls.		schizophrenia. Altered patterns of activity are potentially related to patients with schizophrenia being at their cognitive limits at lower levels of load.		
6.	Described above	Described above	Behaviour: Described above EEG: Only alpha and gamma were implicated during the retention phase. Conclusion: No evidence theta is implicated in retention processes.	Described above	Described above
7.	Described above	Described above	Behaviour: Described above EEG: Theta was not implicated during the retention phase. Conclusion: No evidence theta is implicated in retention processes.	Described above	Described above
Retrieval					
4.	17 female students scoring high in schizotypy (top 3%). Recruited from a pool of 610 students (mean age: 20.7 ± SD: 1.53 years, duration of education:	17 female students scoring average in schizotypy. Recruited from the same pool of 610 students (mean age: 20.07 ± SD: 2.02 years, duration of education:	Behaviour: Participants scoring highly on the K-SPQ responded significantly slower and less accurately to old items compared to control participants. EEG: No significant effects of group were identified for TBA. Participants with high K-SPQ scores had significantly greater theta PLVs between anterior and posterior regions compared to participants with low K-SPQ scores during all time windows.	Strengths: i) Endophenotypic approach limits impacts of patient factors (e.g. medication, length of illness) that typically confound patient research. Limitations: i) Group differences identified through post-hoc pairwise comparisons rather than higher order analysis. ii) Continuous recognition paradigm making it difficult to	Selection i) No Star ii) One Star iii) One Star iv) No Star Comparability i) Two Stars Exposure i) No Star ii) One Star iii) No Star

	14.20 ± SD: 1.86 years).	13.07 ± SD: 1.98 years)	Theta PLVs and behavioural measures were not significantly correlated in any time window. Conclusion: These findings highlight that deficits similar to those observed in patients can be observed in schizotypal individuals.	differentiate processes contributing to successful performance.	**Total: 5/9**
6.	Described above	Described above	Behaviour: Described above EEG: PwS showed significant mean magnitude reductions in evoked theta-activity compared to control participants. Induced theta was reduced for PwS compared to control participants. Conclusion: Results suggest that WM deficits in PwS are associated with impaired oscillatory activity, including theta, during retrieval.	Described above	Described above
7.	Described above	Described above	Behaviour: Described above EEG: Considering theta signal power, no significant effects of schizotypy were found. Considering the theta PLV, no main effect of schizotypy or WM load was identified. Conclusion: Limited evidence for the role of theta in retrieval obtained here.	Described above	Described above

The wide range of stimuli used makes comparing outcomes difficult considering stimuli-specific patterns of EEG activity have been identified (e.g. Doidge, Evans, Herron, & Wilding, 2017; Galli & Otten, 2010). Notably, the two studies using BORTS (6, 7) did not find evidence that theta contributes to retention processes. In addition to these possible stimuli differences, it is noted that in comparison to the others studies (6) and (7) recruited participants that limited the impact of certain patient factors (e.g. duration of illness, medication). This could also have contributed to the observed discrepancy between studies.

Considering the studies that did indicate theta contributed to retention processes (1, 2, 3, 5), the most consistent outcome seems to be more left-lateralised distributions of theta-activity for people with schizophrenia compared to control participants (1, 2, 3). For (1) and (2), theta-power was the EEG measure of interest. For (3) theta event-related de-synchronisation was the MEG measure of interest. Whilst it is difficult to translate findings across different methods, considering: i) for (1) theta-power was coupled with activity in brain networks as identified via fMRI pre-encoding, and ii) MEG is potentially less sensitive to mid-frontal theta (Srinivasan, Winter, & Nunez, 2006); the consistent distribution of effects across studies is strong evidence for their reliability and validity.

Considering the NOS (Wells et al., 2000), three studies achieved four stars (2, 6, 7); the others achieved five, six and seven stars respectively (5, 1, 3). Notably, two of the lowest scoring studies (6, 7) suggested that theta was not implicated in retention processes. Importantly, all studies lost stars (to varying extents) due to their limited definition of exposure and their description of the recruitment process. Thus, the generality of these findings are questionable

considering it is difficult to ascertain the target population and how representative these samples are.

Retrieval

Three studies included in this review considered theta-activity during retrieval (4, 6, 7). Two of these studies (4, 7) adopted an endophenotypic approach by collecting measures of schizotypy and comparing those with high and low scores. The other (6) collected data from those with early onset schizophrenia and compared their data to control participants. All studies collected EEG data. Two studies used DMTS using BORTS as stimuli (6, 7). By contrast, (4) used a verbal continuous recognition memory paradigm, using Korean words as stimuli. Using BORTS as stimuli rather than words has the advantage that they are novel and difficult to verbalise; thus minimising the impact of previous experience on the obtained data. Crucially however, by the nature of the design of the continuous recognition paradigm, it is difficult to differentiate the processes contributing to task performance cleanly. This is less of an issue with the DMTS used in the other studies reviewed.

Across all studies, there was a general pattern that behavioural performance was poorer for those higher in schizotypy or for people with schizophrenia compared to control groups. Most consistently, poorer accuracy was observed. Though (4) also reported slower RTs to old words for people higher in schizotypy.

There is mixed evidence for the relevance of theta-activity during retrieval. (7) identified no significant effects with measures of theta-activity. (4) did not find any significant effects of theta-power that interacted with group. However,

significant effects were found in relation to theta phase-locking values (PLVs). Those with higher schizotypy scores as measured by the Korean version of the schizotypal personality questionnaire (SPQ; Moon, Yang, Lee, Kim, & Ham, 1997; Raine, 1991) were found to have increased theta PLVs for all time windows compared to those with lower schizotypy scores. Theta PLVs were not found to correlate with behavioural memory performance however (4). By contrast, (6) found mean magnitudes for early evoked theta were significantly reduced for patient compared to control participants. Similarly, mean magnitudes for later induced theta were reduced for patient compared to control participants. Finally, anterior early evoked theta magnitudes were found to correlate with behavioural memory performance for control, but not for patient participants (6).

Two studies achieved four stars (6, 7) and one achieved five (4) in relation to the NOS (Wells et al., 2000). All studies lost stars in relation to their definition of exposure and their description of recruitment, impacting the extent to which these samples can be considered representative of the target population. Consequently, these results should be considered with caution.

Discussion

The aim of this review was to understand the evidence that: i) theta-activity contributes to encoding, retention and retrieval processes specifically, and ii) that theta-activity during these respective phases differs for people with schizophrenia compared to control participants. Seven papers were included in this review. Of these seven papers, two reported theta-activity in relation to encoding; five in relation to retention and three in relation to retrieval. Notably, all these papers used variants of WM tasks, rather than EM tasks.

There is limited evidence that theta-activity is implicated during encoding and retrieval. There is mixed evidence that theta-activity is implicated during retention. In relation to the second question, evidence for differential theta-activity during encoding and retrieval between people with and without schizophrenia is limited: only one, low quality paper seemed to suggest this was the case. There was more evidence for differential theta-activity during retention; specifically that people with schizophrenia compared to those without schizophrenia seemed to exhibit increased theta-activity over left-lateralised scalp locations. Furthermore, there was some evidence that this activity may contribute to memory performance. There was limited evidence that patterns of theta-activity observed in people with schizophrenia were identified in those with high schizotypy scores.

Watrous and Ekstrom (2014) advocated that context (re)instatement across multi-layered neural assemblies facilitates encoding, retention and retrieval. Notably, the authors proposed that sustained frequency-specific activity during retention contributed to the likelihood that information will be effectively encoded; increasing the likelihood that this information will be available for retrieval. Nyhus and Curran (2010) highlighted that theta-specific activity has been implicated in these processes. Such assertions are in keeping with extensive animal and human studies demonstrating that pyramidal neurons, are responsive to theta-specific activity (Nunez & Srinivasan, 2006); cell populations known to be prevalent in neocortical and hippocampal structures which have been demonstrated to be highly implicated in WM and EM (e.g. Scoville & Milner, 1957; Vargha-Khadem et al., 1997; Yonelinas, 2002).

The data from this review provide some evidence to support the assertion that theta-activity supports retention processes, and contributes to the likelihood

this information will be encoded. Some studies however (3, 7), advocated that other frequencies, specifically alpha- and gamma-activity may be more strongly associated with this stage of memory processing. Considering the low quality of the studies included in this review however, these findings should be held lightly. Especially considering Basar and Guntekin (2013) finding alpha- and gamma-activity were inconsistently implicated in WM performance. Whilst these findings may appear inconsistent with the findings of Nyhus and Curran (2010), Watrous and Ekstrom (2014) do not make strong assertions about frequency-band specific-activity in relation to WM or EM, and thus these findings do not necessarily contradict this theory. Importantly, these findings highlight the importance of high quality studies addressing broader frequency-ranges to better understand the ways in which frequencies may interact to facilitate memory processes. Basar and Guntekin (2013) similarly concluded there was a need for future research to consider broader frequency ranges.

In light of the limited evidence for theta-involvement during encoding and retrieval, and especially the lack of comparisons between patterns of activity at these stages of memory, the outcomes of the present review are limited in their ability to make assertions about the importance of context-reinstatement and how such patterns may differ for people with schizophrenia. This highlights the need for more explicit investigations addressing this possibility. As previously discussed, there are methodological factors which complicate such investigations; for example the competing requirements of analysing behavioural and EEG data (Luck, 2005). This does not negate the importance of such pursuits however.

The quality of studies included significantly limits the strength of these conclusions; and thus the extent to which these findings can test theories of WM and EM, such as SCERT (Watrous & Ekstrom, 2014). The NOS (Wells et al., 2000) highlighted that few studies included in this review were of high quality across all domains. Most commonly, studies scored more highly on 'selection' and 'comparability', but lacked sufficient information to fulfil the 'exposure' portion of this measure. For example, none of the studies in this review discussed the response rates and whether these varied between groups. Response rates inform the representativeness of samples in a study, and guide the generality of the findings obtained. The lack of this information raises questions about these two aspects of the data. Queries of sample representativeness could explain some of the inconsistencies identified for encoding and retrieval. Moving forward, this suggests clearly defining exposure should be an important criterion for studies.

Basar and Guntekin (2013) proposed that event-related theta to stimuli in WM paradigms were reduced for people with schizophrenia compared to control participants. This seems to contradict the evidence here, where theta-activity was increased. Notably however, this finding related specifically to activity during retention. No such process-differentiation was made by Basar and Guntekin (2013), probably due to the tasks that were included in their review (e.g. oddball tasks). By not employing tasks that permit process-differentiation, it is difficult to attribute poor behavioural task performance to one, all or the integration of the multiple processes that contribute to these outcomes (Lesh et al., 2011). Without understanding the mechanisms underlying observed memory deficits in people with schizophrenia, we are limited in our ability to develop targeted interventions

to remediate these difficulties. Most importantly, this review has highlighted there is limited understanding of the relationship between these measures and memory performance and/or functional outcomes. Future research would benefit from addressing this significant gap in the literature.

This review highlighted inconsistencies between studies employing endophenotypic and case-control approaches. This potentially raises questions about the utility of endophenotypic approaches. The principal argument for adopting endophenotypic approaches is that there is evidence to suggest psychotic experiences are experienced by the general population (e.g. Kendler, Gallagher, Abelson, & Kessler, 1996; Sidgwick, Johnson, Myers, Podmore, & Sidgwick, 1894). Other researchers have argued however that this does not necessitate that these experiences are qualitatively comparable to those experienced by people with schizophrenia (Lawrie, Hall, McIntosh, Owens, & Johnstone, 2010). Specifically, Lawrie et al. (2010) advocated that endophenotypic approaches focusing on individual symptoms have limited generality to people with schizophrenia, considering such diagnoses are based on multidimensional factors that vary across time and contexts. Despite the criticisms, there are advantages to employing these approaches. For example, patient studies are often resource-intensive. Thus, continuous approaches offer one way of developing and refining hypotheses that can subsequently be tested in patient populations (Kwapil & Barrantes-Vidal, 2015). Importantly, these arguments do not undermine the need for further research to better understand the relationship between schizotypy and schizophrenia.

Searching multiple databases with the above eligibility criteria identified only a handful of papers to be synthesised for this review. Despite the intention

being to identify studies addressing EM, mostly those employing WM tasks were identified. At first glance, this may raise questions about the search terms. However, several scoping searches were conducted. These revealed a dearth of studies investigating theta-activity in relation to encoding and retrieval processes. Thus, the search terms were expanded to include those investigating theta-activity in relation to retention as well. Support for the dearth of studies investigating encoding and retrieval specifically has been highlighted in the outcome of this review. The absent and/or inconsistent evidence identified for the involvement of theta-activity for either encoding or retrieval processes brings to mind two possibilities: there is no evidence of theta-activity being implicated in these processes, or differential theta-activity between people with and without schizophrenia during these stages of processing. Given the positive publication bias (Chambers, 2013), studies finding non-significant differences between groups are unlikely to be published, and thus this could explain the dearth of studies. Alternatively, these represent novel research questions for further investigation. Irrespective of which could be true, this outcome highlights the importance of pre-registered reports to scientific investigation, and particularly to the question of whether people with and without schizophrenia exhibit differential theta-activity during encoding and/or retrieval (Chambers, 2013).

Relatedly, the studies included in this review used different stimuli and/or memory tasks. Ideally, this review would have focused on particular stimuli and tasks to avoid differences in results being attributable to these factors. This was not possible here however, given the limited numbers of papers identified in the scoping searches. Similarly, included studies used different methods and measures to examine theta-activity some of which were not directly comparable,

thus limiting the strength of conclusions that can be drawn here. Finally, whilst efforts were made to identify ‘grey’ literature (e.g. conference abstracts) to help overcome the positive publication bias, none of these sources met inclusion criteria. It could be the case that further literature that is relevant this literature search exists, but was not identified with the current search strategy.

Conclusion

This review investigated whether theta-activity contributed to encoding, retention and retrieval processing and whether theta-activity at these processing stages differed between people with and without schizophrenia. This review highlighted there is limited evidence available for theta-activity contributing to encoding and retrieval processes, but there was more for retention processes. Available evidence suggests during retention people with schizophrenia demonstrate increased theta-activity over left-lateralised scalp locations and this pattern of activity may be associated with subsequent memory performance. Further research is required to better understand the relevance of these findings to observed deficits in EM, and whether this contributes to functional outcomes for this population.

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Appendix A: Instructions for Contributors of Psychological Bulletin

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Psychological Bulletin ® publishes evaluative and integrative research reviews and interpretations of issues in scientific psychology. Both qualitative (narrative) and quantitative (meta-analytic) reviews will be considered, depending on the nature of the database under consideration for review.

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- critical assessments of the strengths and weaknesses in past research; and
- important issues that research has left unresolved, thereby directing future research so it can yield a maximum amount of new information.

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Dolores Albarracín, Editor
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Examples:

"This meta-analysis strongly suggests that (description of a given psychosocial treatment) is an effective treatment for anxiety, but only if it is of mild to moderate

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Authored Book:

Rogers, T. T., & McClelland, J. L. (2004). Semantic cognition: A parallel distributed processing approach. Cambridge, MA: MIT Press.

Chapter in an Edited Book:

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SCHOOL OF PSYCHOLOGY

DOCTORATE IN CLINICAL PSYCHOLOGY

EMPIRICAL PAPER

Theta-power and memory retrieval: Applications to schizotypy

Trainee Name:	**Amie Doidge**
Primary Research Supervisor:	**Dr. Anke Karl** Strategic Group Lead of the Clinical Psychology Research Group and Mood Disorder Centre
Secondary Research Supervisor:	**Dr. Jennifer Limond** Senior Lecturer and Research Director for DClinPsy, Consultant Clinical Neuropsychologist
Target Journal:	Psychological Medicine
Word Count:	8000 words (excluding abstract, table of contents, list of tables and figures, references, footnotes, appendices)

Submitted in partial fulfilment of requirements for the Doctorate Degree in Clinical Psychology, University of Exeter

Abstract

People with schizophrenia are known to have difficulties with episodic memory (EM). The purpose of this investigation was to examine the relationship between theta-power and: i) behavioural measures of EM performance, ii) event-related potential (ERP) indices of recollection and, iii) measures of schizophrenia symptomatology. In doing so, the aim was to gain a better understanding of the basic neural mechanisms that contribute to successful EM performance, and how these may differ for people with schizophrenia. The present investigation adopted an endophenotypic approach and collected measures of schizotypy from student participants to minimise patient factors that can confound interpretations. Fifty-four participants were asked to complete a reality-monitoring exclusion EM paradigm whilst electroencephalogram (EEG) data were collected. Measures of theta-power and ERPs were time-locked to words presented during the retrieval phase. There was a significant positive correlation between theta-power over Fz between 600-1000ms post-stimulus presentation and estimates of recollection in the imagine condition as well as a significant negative correlation between these measures of theta-power for perceive items and ERP indices of recollection for imagine items. There was also a significant positive correlation between measures of frontal theta-power in the imagine condition and negative schizotypy. The epoch employed means it is likely these measures of theta-power reflect processes contributing to the content-specific retrieval of imagined items, and post-retrieval processes acting in service of differentiating imagined items in EM. Results are discussed in terms of suggestions for interventions and directions for future research.

Introduction

Meta-analyses have identified episodic memory (EM) as one of the most profoundly affected cognitive domains for people with schizophrenia (Aleman, Hijman, de Haan, & Kahn, 1999; Heinrichs & Zakzanis, 1998; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). EM refers to the ability to consciously remember events and associated details, such as time, place, people or emotions (Tulving, 1972). Arguably however, there are multiple processes that contribute to successful memory performance at different stages; namely encoding, retention and retrieval. The systematic review conducted as part of this thesis highlighted a dearth of EEG studies employing time-frequency analysis approaches to investigate encoding and retrieval specifically in people with schizophrenia. As a first-step to addressing this, the current paper will consider processes that contribute to EM retrieval specifically, and the evidence that these processes operate differently in people with schizophrenia. Through better understanding the ways in which EM retrieval processes operate in people with schizophrenia, more effective and targeted interventions can be developed to alleviate observed difficulties.

Neural activity is known to underlie cognition, and recorded activity can be characterised in terms of magnitude (size) and phase (position on a waveform at a given point in time; Makeig, Debener, Onton, & Delorme, 2004). Specifically, activity arising from neocortical and medial temporal lobe structures, in particular the hippocampus, is known to be implicated in EM; as evidenced by brain lesion studies in both animals and humans (e.g. Nyhus & Curran, 2010; Scoville & Milner, 1957; Vargha-Khadem et al., 1997; Watrous & Ekstrom, 2014; Yonelinas, 2002). Such studies highlight that different brain regions are formed of different

types of neurons (excitatory and inhibitory); pyramidal cells are excitatory cells that constitute the majority of neurons in the aforementioned brain regions (Nunez & Srinivasan, 2006). Furthermore, specific neurons have a tendency to fire at certain frequencies, and different frequencies have been associated with particular cognitive functions. Two frequencies in particular have been implicated in EM; theta (4-7Hz) and gamma (25-100Hz; Nyhus & Curran, 2010; Watrous & Ekstrom, 2014).

A review conducted by Nyhus and Curran (2010) indicated that when recording neural activity, power (magnitude squared) in both theta- and gamma-frequencies during encoding has been found to increase over posterior scalp locations for items that are successfully recalled compared to those that are subsequently forgotten. These increases in theta- and gamma-power are similarly observed during successful EM retrieval (Nyhus & Curran, 2010). Theta-activity was also found to modulate gamma-activity over anterior scalp locations during multiple stages of EM. Nyhus and Curran (2010) proposed that theta- and gamma-activity interact transiently within cortico-hippocampal circuitry to encode and retrieve information. Notably, they advocated that gamma-activity contributes to binding features into coherent, episodic representations, and theta-activity temporally organises these representations. Neural feedback within cortico-hippocampal circuits then serves to reinstate these representations during retrieval. Most importantly, this highlights the importance of reinstating neural activity established during encoding at retrieval to ensure successful performance. The term context-reinstatement is often used to describe comparable patterns of activity observed during encoding and retrieval (Watrous & Ekstrom, 2014). Importantly, here the term context refers to both internal states

and external environmental cues that drive neural activity (Watrous & Ekstrom, 2014). Whilst there is little debate about the importance of context-reinstatement for EM retrieval, less is known about how such contexts are established in the first place.

The spectro-contextual encoding and retrieval theory (SCERT; Watrous & Ekstrom, 2014) is a translational model of EM that can also be applied to working memory (WM). It proposes that signals from the environment are inherently rhythmic, for example natural speech and sounds (Singh & Theunissen, 2003). These rhythmic signals impose frequency- and phase-specific contexts during encoding, potentially causing synapses to fire. When synapses fire, other neurons with similar receptive properties are also likely to fire, thus helping to establish functional cell assemblies (Narayanan & Johnston, 2007). Cross-frequency coupling and phase-synchrony are two mechanisms that determine the strength of synaptic connections within these functional cell assemblies and thus the extent to which environmental signals are encoded; a process known as Hebbian plasticity (Axmacher, Mormann, Fernández, Elger, & Fell, 2006; Canolty & Knight, 2010; Hebb, 1949). Here, the term cross-frequency coupling refers to the interaction between magnitude changes in faster frequencies and the phase of slower frequencies (Vanhatalo et al, 2004) and phase-synchrony refers to the magnitude-independent phase-locking between cycles in different frequency-ranges (Tass et al, 1998).

The extent to which activity within these functional cell assemblies is maintained post-encoding contributes to the likelihood that such patterns of activity can be reinstated (Watrous & Ekstrom, 2014). Reinstatement of activity across assemblies is hippocampally-driven. Assemblies are primed to particular

inputs via the process of encoding; these patterns of activity can be reinstated

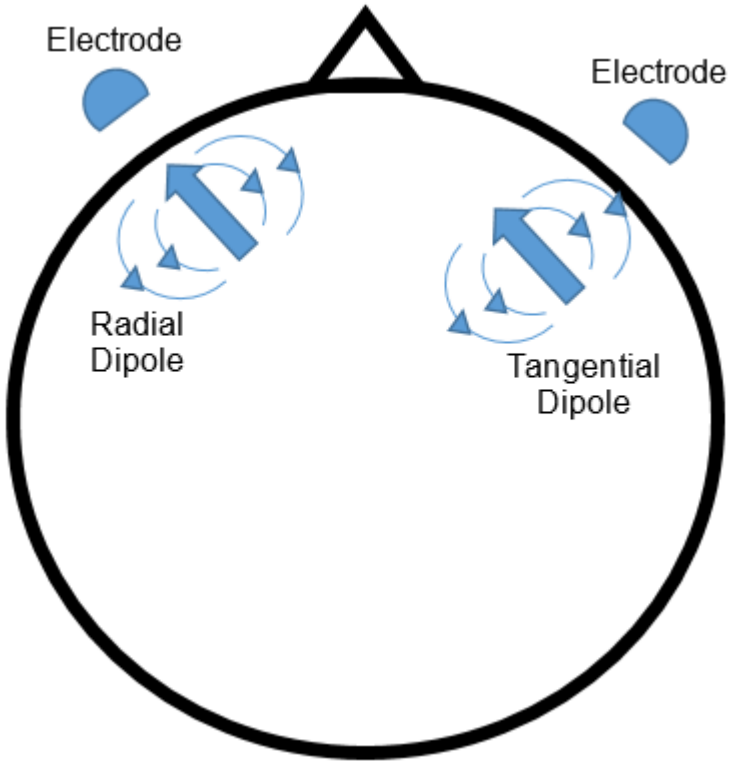

Figure 1 – Diagram of radial and tangential sources. Generally, radial signals are perpendicular and tangential signals are parallel to the scalp.

later when internal or external cues to such inputs are received (Canolty & Knight, 2010; Nadel & Moscovitch, 1997). Taken together, this model provides testable predictions in relation to multiple processes that contribute to EM, including those involved in retrieval.

There are many methods that can be employed to test hypotheses relating to this model. Given their dual frequency- and time-sensitivity, electroencephalography (EEG) techniques may be most suitable. This approach may be preferred over magnetoencephalography (MEG) methods as EEG is sensitive to both radial and tangential neural sources, whereas MEG is only sensitive to tangential neural sources (Hauk, 2013, See Figure 1); theta-activity specifically is hypothesised to originate from radial sources as mid-frontal theta is less commonly observed in MEG studies (Srinivasan, Winter, & Nunez, 2006). It

can be difficult to investigate gamma-activity without specialist equipment to block electrical noise (50Hz), in light of the overlap between activities in these frequency-bands (Luck, 2005). Whilst filters are available to attenuate electrical noise, the use of these should be discouraged as they can distort outcomes, particularly for time-frequency analyses (Cohen, 2014). Consequently, this thesis will consider theta-activity in relation to EM retrieval only.

Beyond time-frequency analyses as discussed above, other EEG indices have been strongly associated with particular cognitive processes involved in EM retrieval; namely recollection and familiarity. Familiarity is often conceptualised as a graded signal strength process that represents the degree of similarity between a current event and a previous experience, in the absence of retrieving contextual information about the prior event (Glanzer, Kim, Hilford, & Adams, 1999; Wixted & Stretch, 2004). For example, you may see someone on the bus you recognise, but are unable to remember their name or where you met. By contrast, the term recollection is often used to describe the recovery of qualitative information about a prior event (Evans & Wilding, 2012; Yonelinas, 2002). According to the dual-process model, recollection is considered to be a threshold-retrieval process (Yonelinas, 2002). Using the above example, you may recall that the person on the bus is Sam whom you met in a bar last Saturday. Often, neural activity relating to these processes are investigated using event-related potential (ERP) methods. This approach assumes that the signal of interest is time-locked to the stimulus and is superimposed over background “noise”. Through averaging it is possible to enhance the signal-to-noise ratio (Pfurtscheller & Lopes da Silva, 1999). The left-parietal old/new effect is a positive deflection in the EEG recording maximal between 500-800ms post-stimulus presentation, with relatively

greater positivity for old compared to new items (e.g. Rugg & Wilding, 2000; Sanquist, Rohrbaugh, Syndulko, & Lindsley, 1980). This index has been strongly associated with the process of recollection as the magnitude of the difference between old and new items has been found to be associated with the amount of contextual information recovered in relation to a studied item (e.g. Vilberg, Moosavi, & Rugg, 2006; Vilberg & Rugg, 2009; Wilding, Doyle, & Rugg, 1995). Therefore, by assessing such indices it is possible to determine the extent to which particular cognitive processes are engaged under specific experimental conditions (for a review of event-related EEG indices in the context of memory research see Wilding & Sharpe, 2003).

EM performance has been shown to be disproportionately compromised when people with schizophrenia are required to: i) organise information during encoding, ii) recollect associations between items, rather than just individual items or iii) complete recall tasks, where participants are not presented with cues to aid memory retrieval, rather than recognition tasks, where participants are presented with cues (Achim & Lepage, 2003; Iddon, McKenna, Sahakian, & Robbins, 1998; Ranganath, Minzenberg, & Ragland, 2008). Considering that recall performance is dependent on the successful recovery of contextual details from the encoding phase (Ranganath et al., 2008), this latter evidence is particularly suggestive of selective deficits in recollection for people with schizophrenia.

Interestingly, little is known about the relationship between ERP indices and frequency-specific activity. There are several theories about how such EEG phenomena are related; two prominent models being *additive* (Cohen, 2014) and *phase-reset* (Makeig et al., 2002). According to the former, the

neurophysiological activities underlying frequency events are distinct from those that underlie ERPs. This model assumes that frequency events are attenuated in the grand averaging process to generate ERPs as they are part of the background noise, rather than related to the signal generated by the stimulus (Cohen, 2014). By contrast, the latter advocates that ERPs at least partially arise from phase-alignment of ongoing frequencies. It is assumed that the onset of a stimulus triggers particular frequency-bands to reset to specific phase values; this reset could reflect a return to specific neural network configurations in service of neural operations (Makeig et al., 2002). Interestingly, there is some evidence to suggest that changes in power may instigate changes in neuronal firing rate; firing rate is related to phase-position (Haegens, Nacher, Luna, Romo, & Jensen, 2011). Thus, it may be the case that changes in power instigate phase-resetting. There are questions however about whether this model can account for all ERPs, particularly those associated with later cognitive operations (Fell et al., 2004). The present data provide an exciting opportunity to investigate these latter possibilities.

This thesis is a re-analysis. The initial project investigated whether deficits in cognitive control contributed to recollection deficits observed in people with schizophrenia. The premise being that a more parsimonious explanation for multiple cognitive deficits in people with schizophrenia could be a deficit in a higher-order cognitive function, such as cognitive control. In pursuit of this, EEG data were recorded from participants whilst they completed a reality-monitoring version of the exclusion task (discriminating internally or externally generated soures of information; Jacoby, 1991). This task was chosen as it enables estimates of recollection and familiarity to be generated. Furthermore, the EEG

data obtained from participants completing this paradigm indicates the left-parietal old/new effect can be used to make inferences about cognitive control (e.g. Elward & Wilding, 2010; Herron & Rugg, 2003; Rosburg, Mecklinger, & Johansson, 2011). Specifically, the presence of magnitude differences between classes of old items indicates conscious control over the contents of what is retrieved. A reality-monitoring version of this task was utilised as one hypothesis for hallucinations in people with schizophrenia is the failure to discriminate between internal and external sources of information (Frith, 1992); thus encoding contexts pertinent to this hypothesised difficulty were selected. In addition to these behavioural and neural measures, measures of schizotypy, dimensional correlates of schizophrenia symptomatology, were collected. Negative correlations between the neural and symptomatology measures would suggest cognitive control deficits contribute to EM problems associated with schizophrenia. Negative correlations between behavioural estimates of recollection and symptomatology would provide further support that recollection is disproportionately affected for people with schizophrenia. No correlations however, were identified between the neural measures and symptomatology across any of the experiments. Nonetheless, a negative correlation was identified between estimate of recollection and symptomatology in people with schizophrenia. Taken together, this suggests people with schizophrenia do experience problems with their memory but the neural measures investigated did not necessarily provide insight into why this is the case. This may be because the event-related potential (ERP) analysis strategy adopted did not capture the mechanism underlying these difficulties. In light of SCERT (Watrous & Ekstrom, 2014), frequency-specific analyses may provide further information.

Despite our developing understanding of frequency-specific activity in relation to EM retrieval in control participants, little is known about how these processes may differ for people with schizophrenia. The systematic review conducted as part of this thesis identified only three studies investigating theta-activity in retrieval (Choi, Jang, Jung, Kim, & Kim, 2016; Haenschel et al., 2009; Koychev, Deakin, Haenschel, & El-Deredy, 2011). Two studies employed endophenotypic approaches and collected measures of schizotypy, comparing those with high and low scores (Choi et al., 2016; Koychev et al., 2011). Considering theta-power specifically, these two studies did not find any significant differences between participants (Choi et al., 2016; Koychev et al., 2011). By contrast Haenschel et al. (2009), collected data from those with early-onset schizophrenia and found that both early-evoked and later-induced mean theta-magnitudes were reduced for people with schizophrenia compared to control participants. Furthermore, early-evoked theta over anterior scalp locations was correlated with behavioural memory performance for control participants, but not those with people with schizophrenia.

These findings are based on small sample sizes (e.g. 17 participants; Choi et al., 2016), making it difficult to differentiate if the absence of effects can be attributed to studies being under-powered. The discrepancy with Haenschel et al. (2009) could also potentially be accounted for by small sample size. Button et al. (2013) suggested that low-powered studies will occasionally identify significant effects through a combination of sampling variation, random error and thresholds of statistical significance. Thus, it is important to conduct replication studies to verify effects identified in this way. Button et al. (2013) proposed however that it is important to recruit larger sample sizes when attempting to replicate effects

because using similar sample sizes will only achieve approximately 50% power, if the initial effects achieved nominal significance (e.g. p≈0.05). Taken together, this highlights the value in re-analysing the available data from a larger sample to investigate the relevance of theta-power to EM retrieval more broadly, but also the ways in which this may be aberrant in people with schizophrenia.

The purpose of this re-analysis was three-fold. To investigate: i) how theta-power contributes to behavioural EM retrieval performance, ii) the relationship between theta-power and ERP measures of recollection and, iii) the relationship between measures of theta power to positive schizophrenia symptomatology. Notably, the present analyses focus on power, rather than phase measures of theta-activity. This is in light of the findings of Nyhus and Curran (2010) indicating that cross-frequency, rather than within-frequency synchrony, was most important to EM retrieval.

Regarding the first aim, it was hypothesised that there would be a positive correlation between measures of theta-power and the likelihood of discriminating target and new items in each condition (imagine/perceive) at retrieval; as well as estimates of recollection. This is in light of the observed increases in theta-power during encoding and retrieval reported by Nyhus and Curran (2010), and the observed correlation between theta-power and behavioural performance in control participants by Haenschel et al. (2009). Correlations with reaction times (RT) were not conducted as associations between these measures and theta-power have been shown to be modulated by latency of effects (Jacobs, Hwang, Curran & Kahana, 2006) and are thus beyond the scope of the current investigation. Furthermore such associations have been more commonly

associated with decision-making processes acting post-retrieval (Jacobs et al, 2006).

Considering the second aim, it was anticipated that there would be a positive relationship between measures of theta power and an ERP index of recollection. Finally, in relation to the third aim, a negative correlation between measures of positive schizotypy and measures of theta-power was expected. Importantly, data were analysed for each encoding condition separately in accordance with SCERT (Watrous & Ekstrom, 2014) which suggests different internal or environmental stimuli instigate different patterns of neural activity. Thus, for each of the above hypotheses it was anticipated there would be differences between conditions given one hypothesis for hallucinations in people with schizophrenia is that misattribution of internal events as external (Frith, 1992).

Method

Participants

Fifty-four participants (ten male) were recruited from Cardiff University via the SONA research management system; each received £10/hour in exchange for their participation. All participants provided written informed consent and were aware they could withdraw at any point without penalty. All participants reported: i) speaking English as a first language, ii) having normal or corrected-to-normal vision, iii) being right-handed, iv) having no prior diagnosis of dyslexia, and v) not to be taking psychotropic medication. Ten participants were excluded from analyses; five for poor behavioural performance (estimates of discrimination below 0.1; see text below for the discrimination measure that was employed), one

for contributing insufficient EEG trials to ERP analyses (<16), and four for contributing insufficient EEG trials to time-frequency analyses (<16). Of the remaining 44 participants (mean age = 20.57 years; range 18–27 years), seven were male. Ethical approval for the study was obtained from the Cardiff University School of Psychology Ethics Committee (EC.13.01.08.3395; EC.14.03.11.3768) and University of Exeter College of Life and Environmental Science Ethics Committee (eCLESPsy000053 v2.1; see Appendix A).

Overview of Procedure

Data were collected as part of a larger scale investigation and the method has been reported in other publications (Doidge, 2015; Doidge, Evans, Herron, & Wilding, 2017). Only measures relevant to the current research questions are presented here. Participants initially completed the study phase of the exclusion paradigm. Following this, participants completed the measures of schizotypy: the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; Mason, Claridge, & Jackson, 1995), the 21-item Peters et al. Delusion Inventory (PDI; Peters, Joseph, Day, & Garety, 2004) and the Launay-Slade Hallucination Scale-Revised (LSHS; Launay & Slade, 1981; Morrison, Wells, & Nothard, 2002). When these were completed, the electrode cap was applied and participants completed the test phase of the exclusion paradigm whilst EEG data were acquired. In total, there was a one-hour delay between study and test phases of the exclusion paradigm.

Schizotypy Measures

O-LIFE (Mason et al., 1995). This measure consists of four-subscales that assess the different dimensions that characterise schizotypy: unusual

experiences (positive schizotypy), introvertive anhedonia (negative schizotypy), cognitive disorganisation (disorganised schizotypy) and impulsive non-conformity. This latter subscale however is not consistent with the three-factor model of schizotypy (e.g. Arndt, Alliger, & Andreasen, 1991; Liddle, 1987), and thus was not consider further in these analyses. The O-LIFE has both high internal validity ($\alpha = 0.77$; Mason et al., 1995) and test-retest reliability (smallest $r(28)=0.76, p<0.001$; Burch, Steel, & Hemsley, 1998).

PDI (Peters et al., 2004). This measure assesses positive schizotypy, specifically the extent to which people endorse various delusional beliefs and the amount of distress caused, preoccupation with and strength of conviction in such beliefs. The PDI has high internal validity ($\alpha = 0.82$; Peters et al., 2004) and test-retest reliability (smallest $r(68)=0.78, p<0.001$; Peters et al., 2004).

LSHS (Launay & Slade, 1981; Morrison et al., 2002). This measure assesses positive schizotypy, specifically proneness to experiencing vivid thoughts and daydreams as well as visual and auditory hallucinations. The LSHS has been found to have good test-retest reliability ($r(116)=0.84, p<0.001$; Bentall & Slade, 1985).

Exclusion Paradigm

Stimuli. Four hundred and eighty six picture-word pairs were selected from the International Picture Naming Project database (http://crl.ucsd.edu/experiments/ipnp/). Words were selected based on the following criteria: i) frequency range of one to nine per million, ii) three to ten letters in length. According to the values reported in the database, the mean percentage naming frequency of selected picture-word pairs was 86%. All words

were presented in white Times New Roman font on a black background at a viewing distance of 1.2m. Words subtended maximum visual angles of 0.8° (vertical) and 5.6° (horizontal). The pictures were black line drawings subtending maximum visual angles of 12.3° (vertical) and 10.5° (horizontal) and were presented on a white background. Stimuli were presented using E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA).

Design. Three hundred and sixty picture-word pairs were randomly selected and sorted into three lists (120 picture-word pairs/list). Study phases were comprised of two picture-word lists (240 picture-word pairs); one list for each condition (imagine and perceive). Test phases were comprised of all three lists (360 picture-word pairs). Test phases were divided in half, with a 5-minute break in between. An equal number of new (unstudied) and studied items from each condition (imagine and perceive) were presented in each half of the test phase. The remaining 126 picture-word pairs were used as filler items, and were presented during study phases only (63 picture-word pairs per condition; 26 at the beginning and 100 at the end of this phase). Filler items were constant for all participants. Twelve versions were programmed to counterbalance the following factors: i) word list appearing as new (unstudied) and studied items in each condition (imagine and perceive), ii) response hand at test, and iii) class of items (imagine or perceive) first presented as ‘targets’ in test phases.

All study trials had the following structure: fixation cross (500ms), blank screen (300ms), word (300ms), blank screen (150ms), white frame (1500ms), and question mark (3000ms; see Figure 2). Study phases consisted of two trial-types that corresponded to the encoding conditions: imagine and perceive. Participants were unaware of the trial-type until the white frame was presented.

For perceive trials, a black line drawing of the object denoted by the preceding word was presented simultaneously and within the white frame. For imagine trials, only the white frame was presented and participants were asked to imagine a line drawing of the object denoted by the preceding word. During the question mark, participants were asked to rate the quality of the perceived or imagined image (response options: good, fair, poor) via key-press using the index, middle and ring fingers of the right hand respectively. Study trials were terminated by key-press or when 3000ms from the onset of the question mark had elapsed. The next trial commenced after the inter-trial interval (1000ms), during which a blank screen was presented.

All test trials had the following structure: fixation cross (500ms), blank screen (300ms), word (300ms), and question mark (3000ms; see Figure 2).

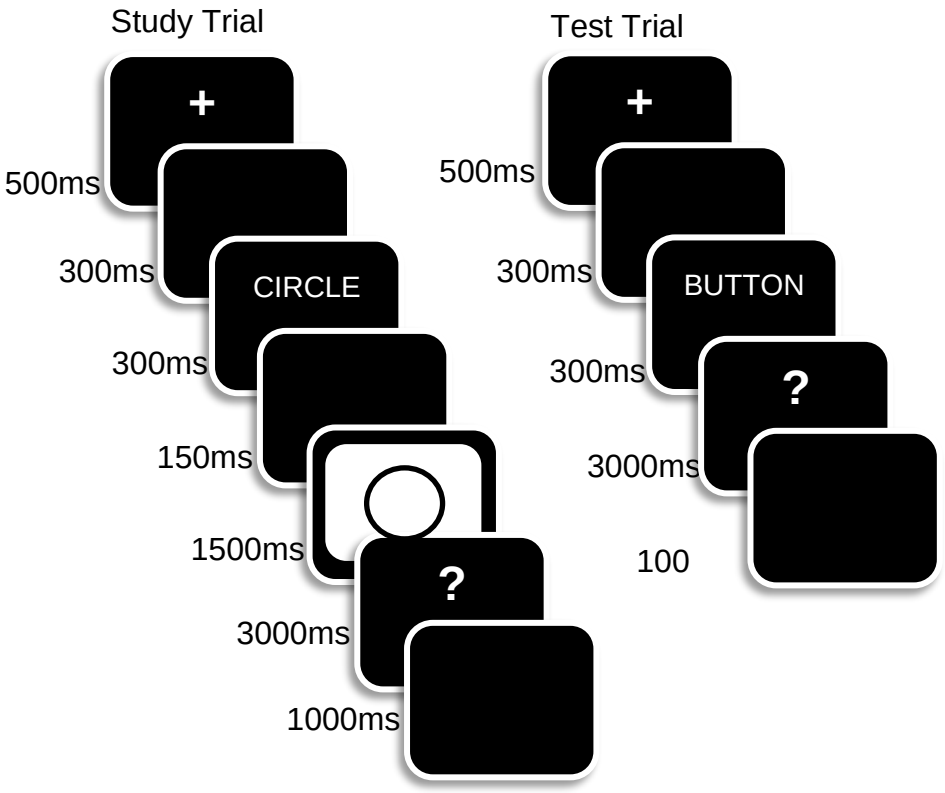

Figure 2 – A schematic representation of the study trials (left) and test trials (right). Figure reproduced from Doidge (2015) and Doidge, Evans, Herron, and Wilding (2017).

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During the question mark participants were asked to make one of two key-presses using the index fingers of each hand: one key for items encountered in one of two encoding conditions (imagine or perceive; designated as targets), another key for new (unstudied) items or items encountered in the alternate encoding condition (designated as non-targets). Test trials were terminated by key-press or when 3000msec from the onset of the question mark had elapsed. The next trial commenced after the inter-trial interval (1000ms), during which a blank screen was presented. Target designations were changed at the end of the first half of the test phase.

EEG Acquisition

EEG data were recorded using BrainVision Recorder (Version 1.20.0601) from 25 silver/silver chloride electrodes embedded in an elasticated cap, with two further electrodes placed on left and right mastoids. Electrode locations were based on the International 10-20 system (Jasper, 1958) and covered midline (Fz, Cz, Pz), fronto-polar (Fp1/Fp2), frontal (F7/8, F5/6, F3/4), central (T7/8, C5/6, C3/4), parietal (P7/8, P5/6, P3/4) and occipital sites (O1/2). Additional bipolar electrodes placed above and below the right eye (vertical electro-oculogram [VEOG]) and on the outer canthi (horizontal electro-oculogram [HEOG]) were used to record eye-movements. EEG and EOG were recorded at 250Hz using a bandpass filter between 0.03-40Hz and an averaged reference.

ERP Pre-processing

BrainVision Analyzer (Version 2.0.4.368) was used to analyse the data. Data were re-referenced offline to the linked-average signal at the mastoids. EOG blink artifacts were corrected using the Gratton, Coles, and Donchin (1983)

algorithm. Trials containing: i) large EOG artifacts post-correction, ii) muscular activity, iii) A/D saturation or, iv) baseline drift exceeding ±75μV were rejected. For ERP analysis, data were segmented into 1700ms epochs, with a 200ms pre-stimulus baseline relative to which all mean amplitudes were calculated. Mean trial numbers across participants (range in parentheses) that contributed to each condition of interest were as follows: imagine target = 43 (20-58), perceive target = 42 (19-56), imagine new = 52 (33-60) and perceive new = 52 (24-60). This analysis has been previously reported by Doidge (2015). Mean trial numbers have been adjusted for the sample reported here.

Theta-Power Pre-processing

BrainVision Analyzer (Version 2.1.2.327) was used to analyse the data. Comparably to ERP pre-processing steps, data were re-referenced offline to the linked-average signal at the mastoids. EOG artifacts were corrected using the independent component analysis algorithm (Jung et al., 2000). Data were segmented into 4000ms epochs, with a 1000ms pre-stimulus period. Trials containing: i) large EOG artifacts post-correction, ii) muscular activity, iii) A/D saturation or, iv) baseline drift exceeding ±75μV were rejected. To confirm the presence of theta-activity specifically, a continuous wavelet transform was applied using complex Morelet Wavelet to each trial for each participant in order to extract wavelet coefficients (frequency range = 2 – 45Hz; frequency steps = 30; Morelet parameter = 5; Morelet, Arens, Fourgeau & Glard, 1982; Tallon-Baudry, Bertrand, Peronnet & Pernier, 1998). Frequency steps increased logarithmically from 0.8 at the lowest frequency (2Hz) to 18.0 at the highest frequency (45Hz). Data were baseline corrected using 200ms of data from -300 to -100ms pre-stimulus presentation, to avoid contamination with neural activity

related to the on/offset of stimuli, including the fixation cross. Once theta-activity had been confirmed by visual inspection (see Figure 3), a complex demodulation algorithm was applied to extract the time-course of power measures in this frequency-range (Draganova & Popivanov, 1999). A frequency-range of 4-8Hz was used for this purpose, given the discrepancy in the literature defining theta

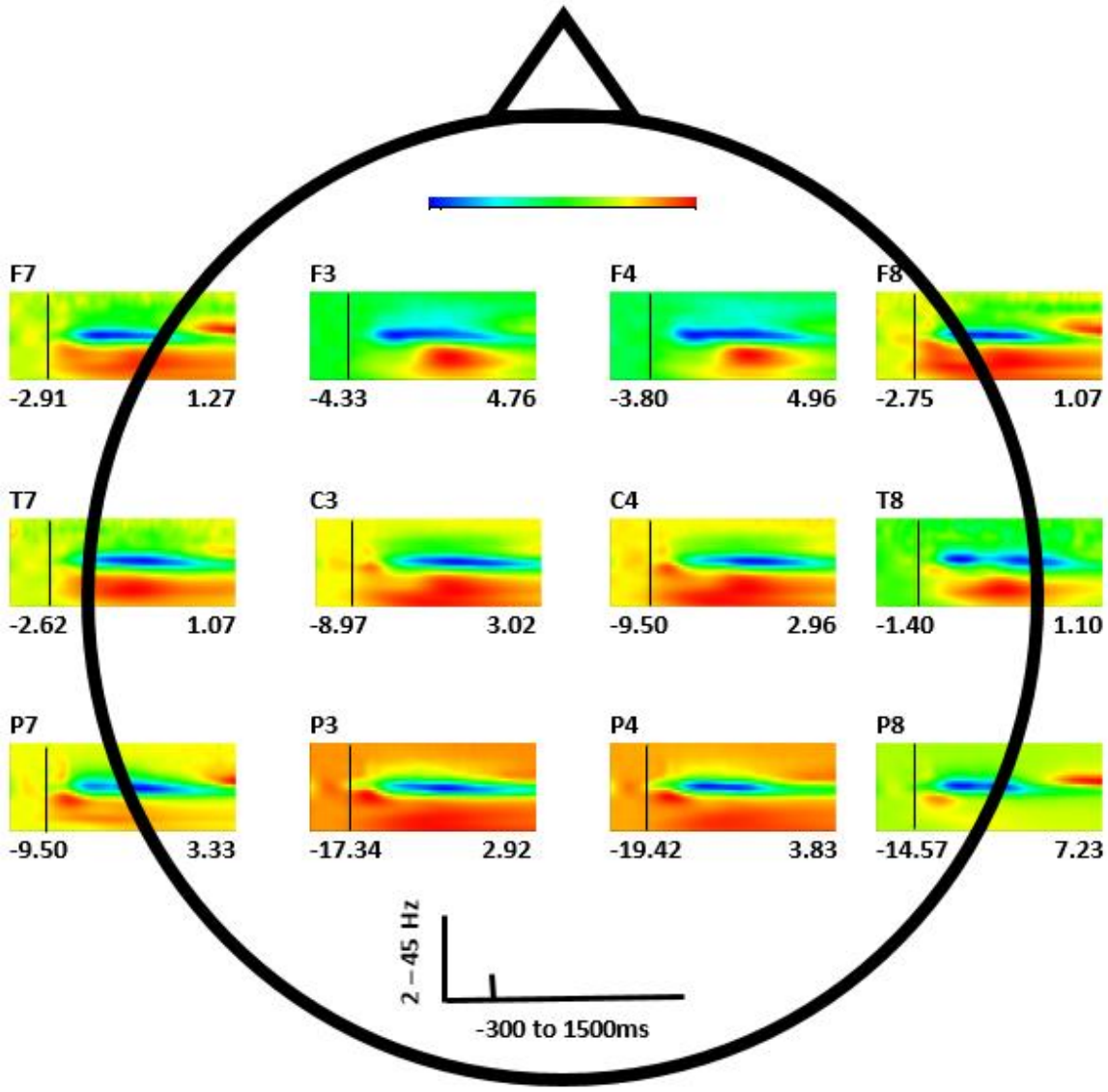

Figure 3 - Power (μV^2) maps averaged across all trials, for all participants for frontal (F7/8, F3/4), central (T7/8, C3/4) and parietal (P7/8, P3/4) scalp locations from -300ms pre-stimulus presentation to 1500ms post-stimulus presentation, from 2-45Hz (logarithmic scale). Numbers under each panel indicate the anchor points for the colour scale. Maps demonstrate increased power in the theta-range (4-8Hz) as well as a decrease in power in the alpha-range (8-12Hz) across a prolonged time period and wide-spread scalp locations.

as 4-7Hz or 4-8Hz. Data were re-segmented from -300 to 1500ms to eliminate edge-effects (Cohen, 2014).

Mean trial numbers across participants (range in parentheses) that contributed to each condition of interest were as follows: imagine target = 42 (22-55), perceive target = 41 (17-56), imagine new = 51 (31-60) and perceive new =

51 (28-59). Importantly, piloting ensured mean trial numbers across conditions are balanced; differential mean trials per condition of interest may have biased analyses (Cohen, 2014).

Analysis Strategy

Behaviour. Snodgrass and Corwin (1988) advocated that two measures of discrimination performance can be calculated: the likelihood of giving a target response to target items minus the likelihood of giving a target response to non-target items (PCorr[target|non-target]) or new items (PCorr[target|new]). According to the procedures outline by Jacoby (1991) estimates of recollection (R) can be calculated across two exclusion conditions using the following formula: R= PCorr[target]–PCorr[non-target]. Target-new discrimination measures (PCorr[target|new]; justification in the ERP section below) and estimates of recollection were calculated for each encoding condition (imagine/perceive) for each participant and were correlated with theta-power (details of how these measures are derived are described below) using Spearman's correlations, given the non-normal distribution of variables (see Appendix B).

ERP. Difference measures were calculated by subtracting mean amplitudes for new items from those for target items for each condition. Mean amplitudes were calculated from 500-800ms post-stimulus presentation over left-parietal electrodes only (P7, P5, P5). Doidge (2015) previously identified this is where effects were largest. Difference measures were subsequently correlated with theta-power for each participant using Spearman's correlations as assumptions of normality were violated (see Appendix B). Analyses were

restricted to target and new items, as correct responses to non-target items can be made with or without memory for these items as a consequence of participants identifying non-target and new items via the same key press. Consequently, analysing difference measures for target items only avoids this potential contamination in the EEG data. Only outcomes from correlational analyses will be reported in relation to ERPs as figures and statistical analyses have previously been reported elsewhere (Doidge, 2015).

Theta-Power. In light of the limited research investigating differential theta-activity during EM retrieval between people with and without schizophrenia, a data-driven approach was adopted (Nigbur, pers. comm.). To determine epochs and scalp locations of interest, once complex demodulation had been applied, all trials regardless of condition of interest were averaged, and topographic maps of effects were produced. Through visual-inspection of these maps, it was possible to identify epochs and scalp locations of maximal theta-power: from 100-300ms post-stimulus presentation over Pz and 600-1000ms post-stimulus presentation over Fz (see Figure 4). Both scalp locations are in keeping with the findings of Nyhus and Curran (2010) emphasising the importance of cortico-hippocampal interactions to EM retrieval. This first epoch was in keeping with hypotheses advocating the potential importance of early power to phase-resetting (Cohen, 2014). Evidence from Doidge et al. (2017) highlighted the importance of frontal activity between 500-800ms to the retrieval of imagine items specifically, and thus this latter epoch is in keeping with this evidence. Consequently, both epochs and locations were adopted for further analyses.

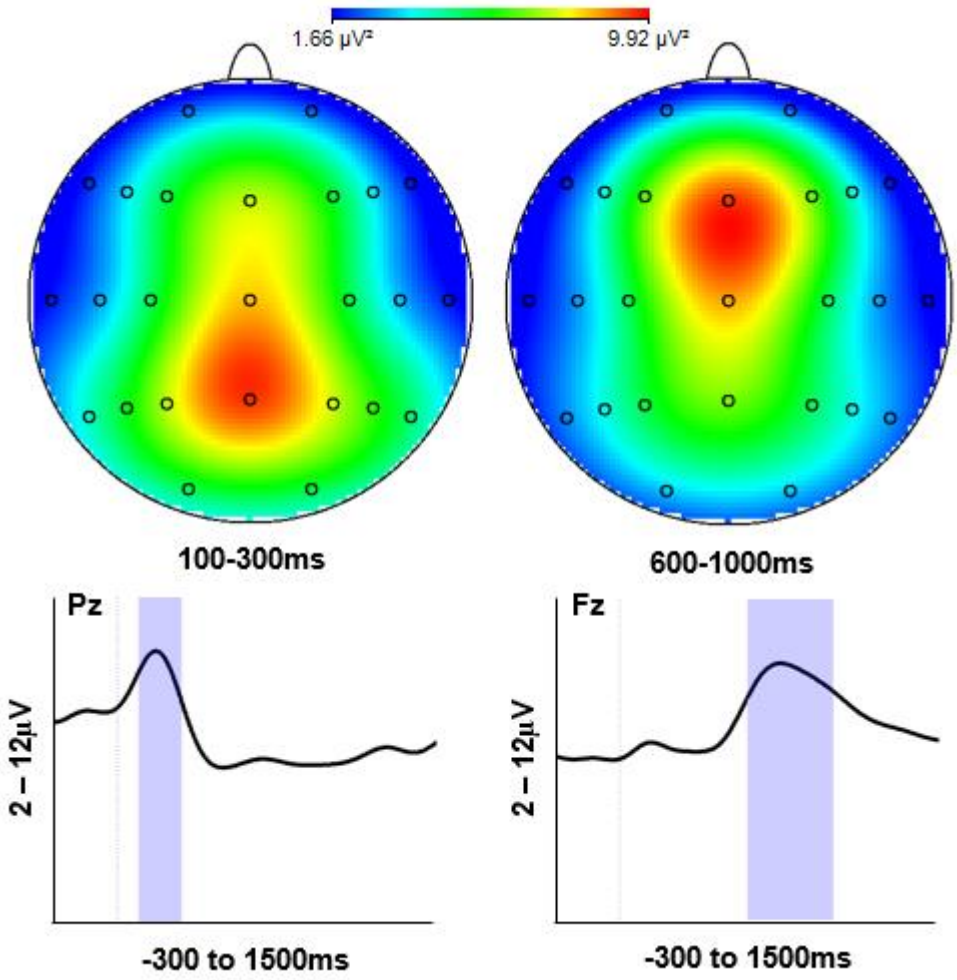

Figure 4 - Topographic maps demonstrating the distribution of theta-power (μV^2) from 100-300ms and 600-1000ms post-stimulus presentation for all participants, across all trial types. Lower panel demonstrates the time-course of theta-power across the whole epoch (-300 to 1500ms). Grey boxes are used to highlight the time windows of interest used for the topographic maps.

Mean theta-power was calculated for target and new items for each condition (imagine/perceive) for each participant. To determine the presence of old/new effects over Pz and Fz, theta-power was entered into two separate ANOVA with factors of condition (two levels: imagine/perceive), target designation (two levels: target/new). Where significant effects involving target designation were identified, difference measures were subsequently calculated by subtracting theta-power for new items from target items in each condition. Justification for calculating difference measures for target items only are highlighted in the above subsection. Mean theta-power difference measures were

then entered into further analyses with measures of schizotypy using Spearman's correlations with measures of positive schizotypy, in accordance with the hypothesis. As an exploratory investigation however, measures of negative and disorganised schizotypy were also included as previous literature has not addressed schizophrenia symptomatology at the level of specific symptoms. Spearman's correlations were used as variables were non-normally distributed (see Appendix B).

Results

Psychometrics

Mean total and subscale scores for each schizotypy measure are reported in Table 1. Where possible, normative values are also reported; for the most part, mean values are in accordance with these. Where there are discrepancies, mean values are still comparable with other studies which have employed these measures (Bradbury, Stirling, Cavill, & Parker, 2009; Evans, Gray, & Snowden, 2007; PDI, O-LIFE and LSHS respectively; Jones & Fernyhough, 2009).

Behaviour

The likelihood of correct responses (PCorr) and reaction times (RT) for each encoding condition, split by target designation are presented in Table 2. For both encoding conditions, the likelihood of correctly giving a target response to target items (PCorr[target|target]) was reliably greater than a target response to non-target items (PCorr[target|non-target]) or new items (PCorr[target|new]; (smallest $t(43)=25.46$, $p<.001$, 95%CI [0.57, 0.67], $dz=0.54$). A 2x2 repeated measures ANOVA on these discrimination measures by encoding condition

revealed only that PCorr[target|new] was superior to PCorr[target|non-target] ($F(1, 43)=50.05$, $p<.001$, $\eta p^2=0.54$).

Table 5 - Mean psychometric scores with standard deviations (SD) in parentheses. Values in bold represent the measures entered into initial correlation analyses. Where possible, normative values have been reported (Mason et al., 1995; Peters et al., 2004; for O-LIFE and PDI respectively). Table has been adapted from Doidge et al. (2017) for this sample.

Measure	Mean (SD)	Min	Max	Normative Value (SD)
O-LIFE				
Unusual Experiences	**5.27 (4.72)**	0	17	9.70 (6.70)
Cognitive Disorganisation	**10.75 (5.04)**	1	22	11.60 (5.80)
Introvertive Anhedonia	**3.98 (3.30)**	0	12	6.20 (4.60)
PDI Total	**37.16 (27.30)**	0	113	58.90 (48.00)
Yes	4.04 (2.61)	0	11	6.70 (4.40)
Distress	10.23 (8.30)	0	36	15.50 (14.10)
Pre-occupation	10.07 (8.16)	0	28	15.40 (14.10)
Conviction	12.84 (8.97)	0	38	20.40 (16.00)
LSHS-R Total	**23.18 (5.32)**	15	38	-
Vivid Thoughts	6.02 (1.53)	3	9	-
Auditory Hallucinations	5.23 (1.39)	4	8	-
Vivid Daydreams	5.16 (2.29)	3	12	-
Visual Hallucinations	6.73 (1.56)	3	11	-

Using the above formula, the following estimates of recollection (R) were obtained for imagine and perceive conditions respectively: 0.59 and 0.54. A paired *t*-test indicated that imagine R was marginally greater than perceive R ($t(43)=2.14$, $p=.038$, 95%CI [0.003, 0.10], $dz=0.32$).

Table 6 - Probabilities of correct responses (PCorr) and reaction times (RT) in milliseconds to target, non-target and new (unstudied) items split by encoding condition (imagine and perceive). Standard deviations (SD) are in parentheses. Hit = correct response, CR = correct rejection (correct response). Table has been adapted from Doidge et al. (2017) for this sample.

Proportion	Imagine (SD)		Perceive (SD)	
	PCorr	RT	PCorr	RT
Target (T) Hit	0.77 (0.11)	1106 (201)	0.75 (0.13)	1036 (169)
Non-Target (NT) CR	0.87 (0.08)	1084 (178)	0.87 (0.07)	1106 (226)
New CR	0.93 (0.07)	1015 (187)	0.94 (0.07)	1009 (203)

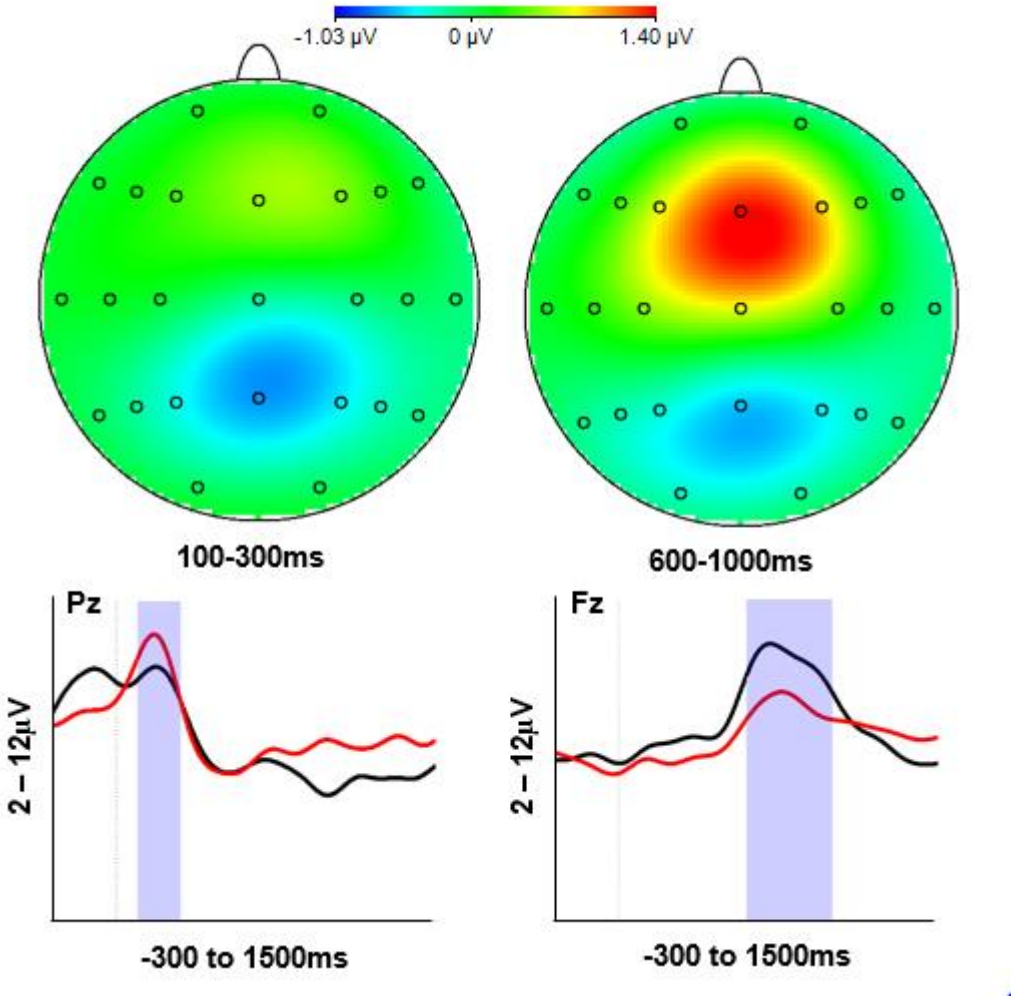

Figure 5 - Topographic maps for the Imagine condition demonstrating the distribution of target-new theta-power differences (μV^2) from 100-300ms and 600-1000ms post-stimulus presentation. Lower panel demonstrates the time-course of target-new theta-power across the whole epoch (-300 to 1500ms). Grey boxes are used to highlight the time windows of interest used for the topographic maps. Black line represents theta-power for target items. Red line represents theta-power for new items

Theta-Power

Figure 5 and 6 shows theta-power for each condition (imagine and perceive respectively), and target designation over Pz and Fz electrode sites. These seem to indicate that effects in both epochs and locations of interest are larger in the imagine, than in the perceive condition. Interestingly, in the early epoch, rather than an increase in theta-power as was hypothesised, there appears to be a decrease in theta-power. Considering the first epoch (100-

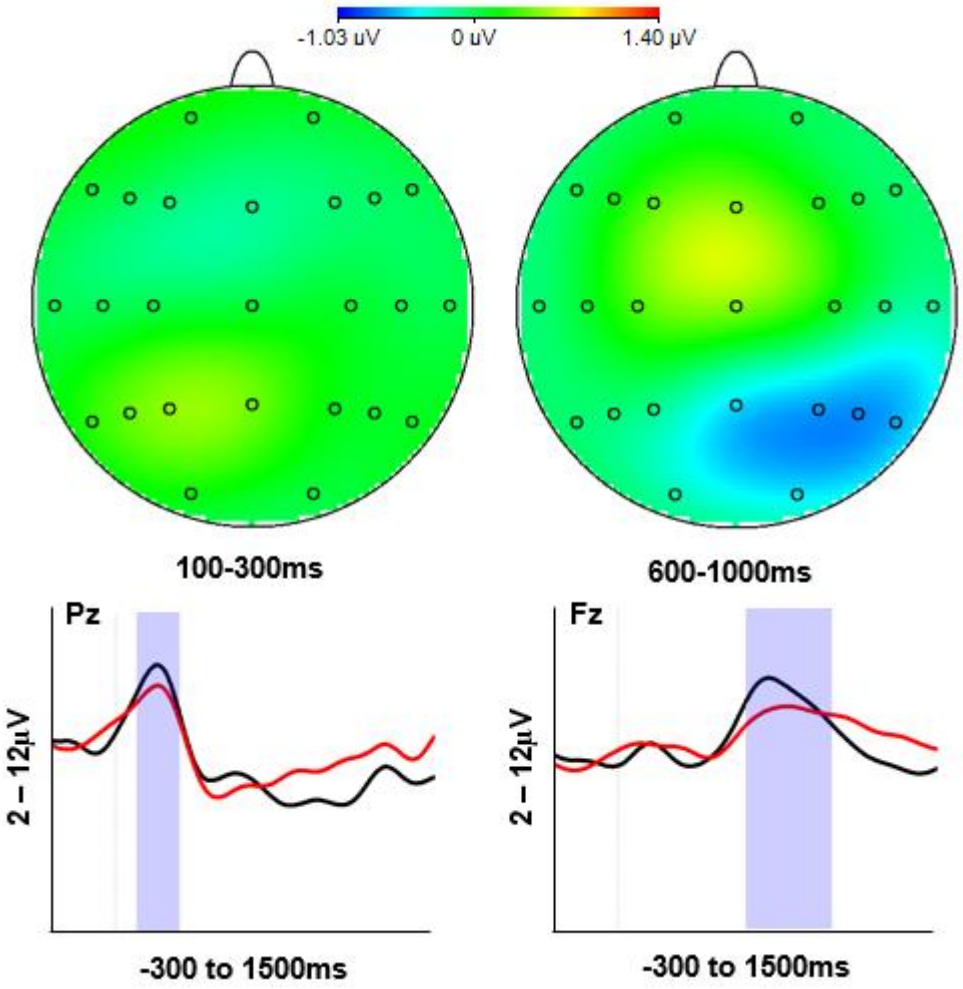

Figure 6 -Topographic maps for the Perceive condition demonstrating the distribution of target-new theta-power differences (μV^2) from 100-300ms and 600-1000ms post-stimulus presentation. Lower panel demonstrates the time-course of target-new theta-power across the whole epoch (-300 to 1500ms). Grey boxes are used to highlight the time windows of interest used for the topographic maps. Black line represents theta-power for target items. Red line represents theta-power for new items.

300ms) and Pz, results from the initial ANOVA however indicated no significant effects or interactions. Considering the second epoch (600-1000ms) and Fz, results from the initial ANOVA revealed only a significant main effect of target designation ($F(1, 43)=13.32$, $p=.001$, $\eta p^2=0.24$), indicating target items elicited greater theta-power than new items ($t(43)=3.65$, $p=.001$, 95%CI [0.44, 1.51], $dz=0.57$). As target-new differences were only identified in the second epoch, only difference measures from this time window and location were entered into further analyses.

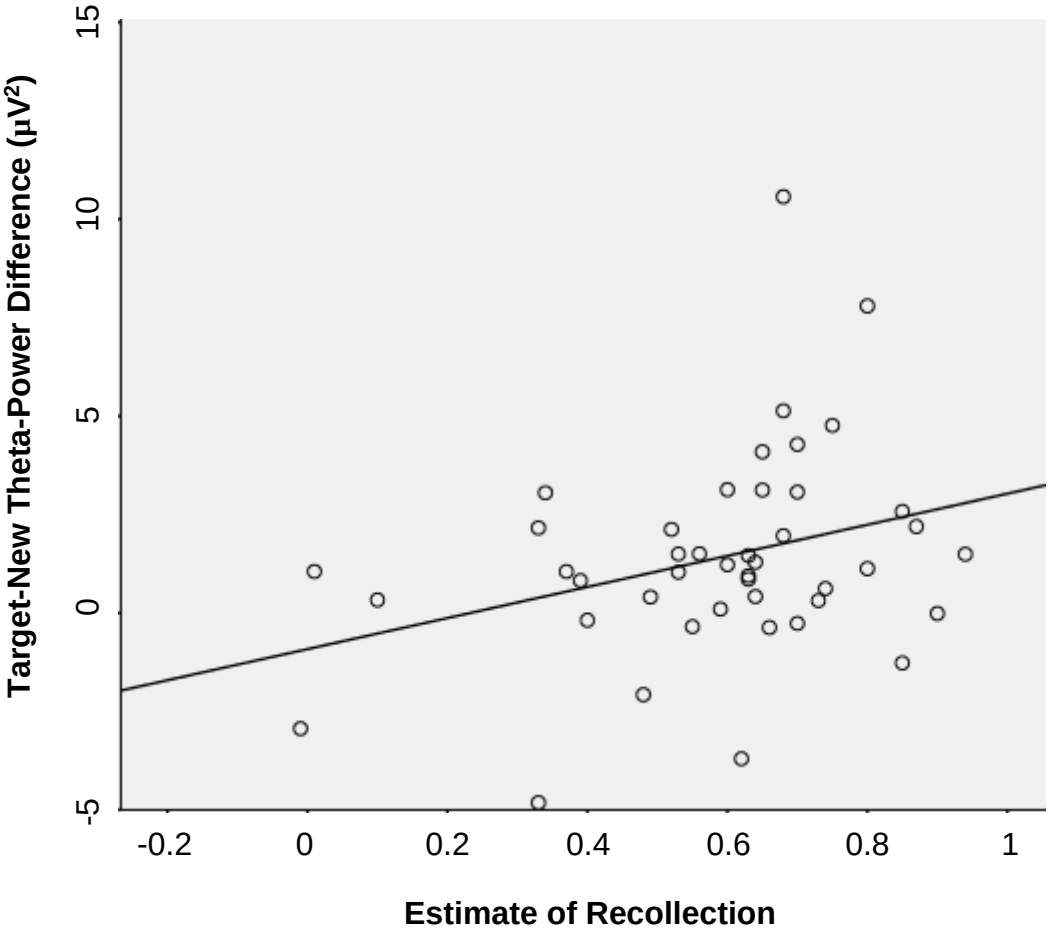

Figure 7 – Scatterplot of theta-power (μV^2) target-new differences against ERP (μV) target-new differences for the imagine condition. Theta-power target-new difference measures are calculated using mean values from Fz, 600-1000ms post-stimulus presentation.

Correlations

Behaviour. The purpose of these analyses were to understand the relationship between behavioural memory performance and measures of theta-power. Target-new discrimination measures and estimates of recollection for each condition (imagine/perceive) were entered into Spearman's correlations with theta-power difference measures. A significant positive correlation was identified between the estimate of recollection and the theta-power difference measure in the imagine condition only ($\rho(42)=0.30, p=.048$; see Figure 7).

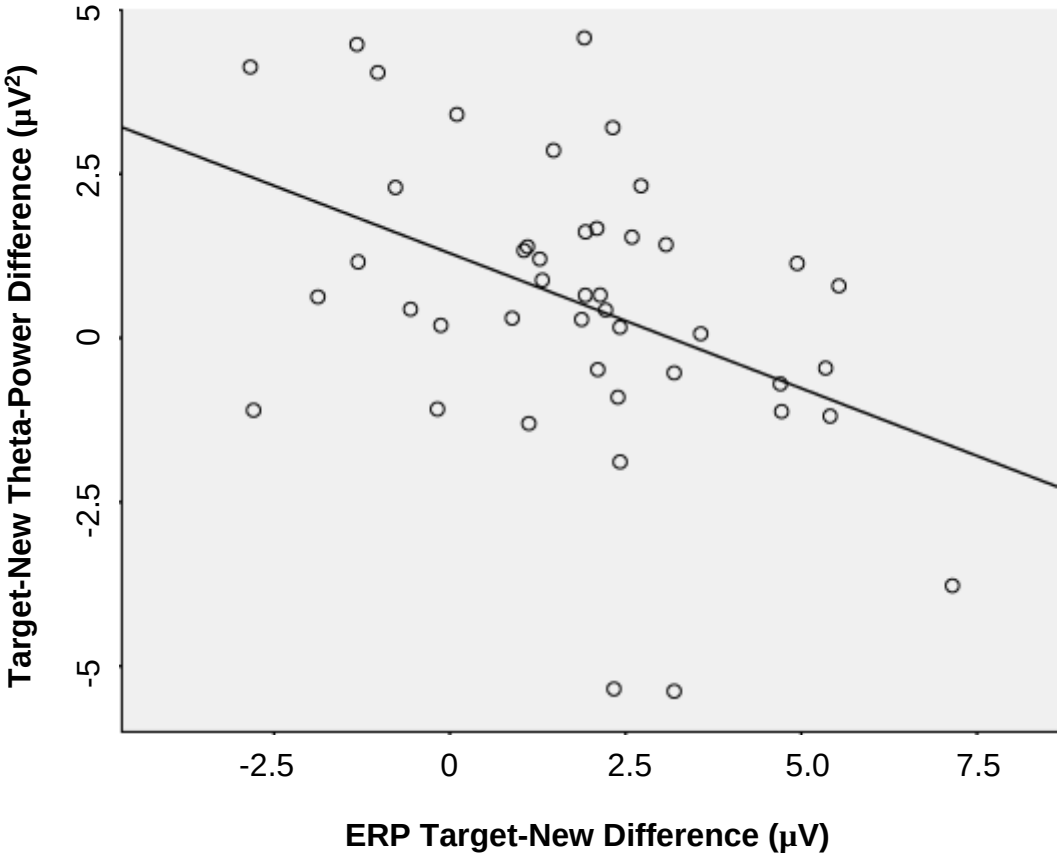

Figure 8 – Scatterplot of theta-power (μV^2) target-new differences for the perceive condition against ERP (μV) target-new differences for the imagine condition. Theta-power target-new difference measures are calculated using mean values from Fz, 600-1000ms post-stimulus presentation. ERP target-new difference measures are calculated using mean values from left, posterior electrode locations (P7, P5, P3).

ERP. These analyses were conducted to gain an understanding of the relationship between theta-power and ERP indices of recollection for each condition (imagine/perceive). When difference measures of theta-power and ERP difference measures were entered into analyses, one significant negative correlation was identified between theta-power difference measures in the perceive condition and the magnitude of the left-parietal old/new effect in the imagine condition ($\rho(42)=-0.41, p=.006$; see Figure 8 for a scatterplot showing this relationship).

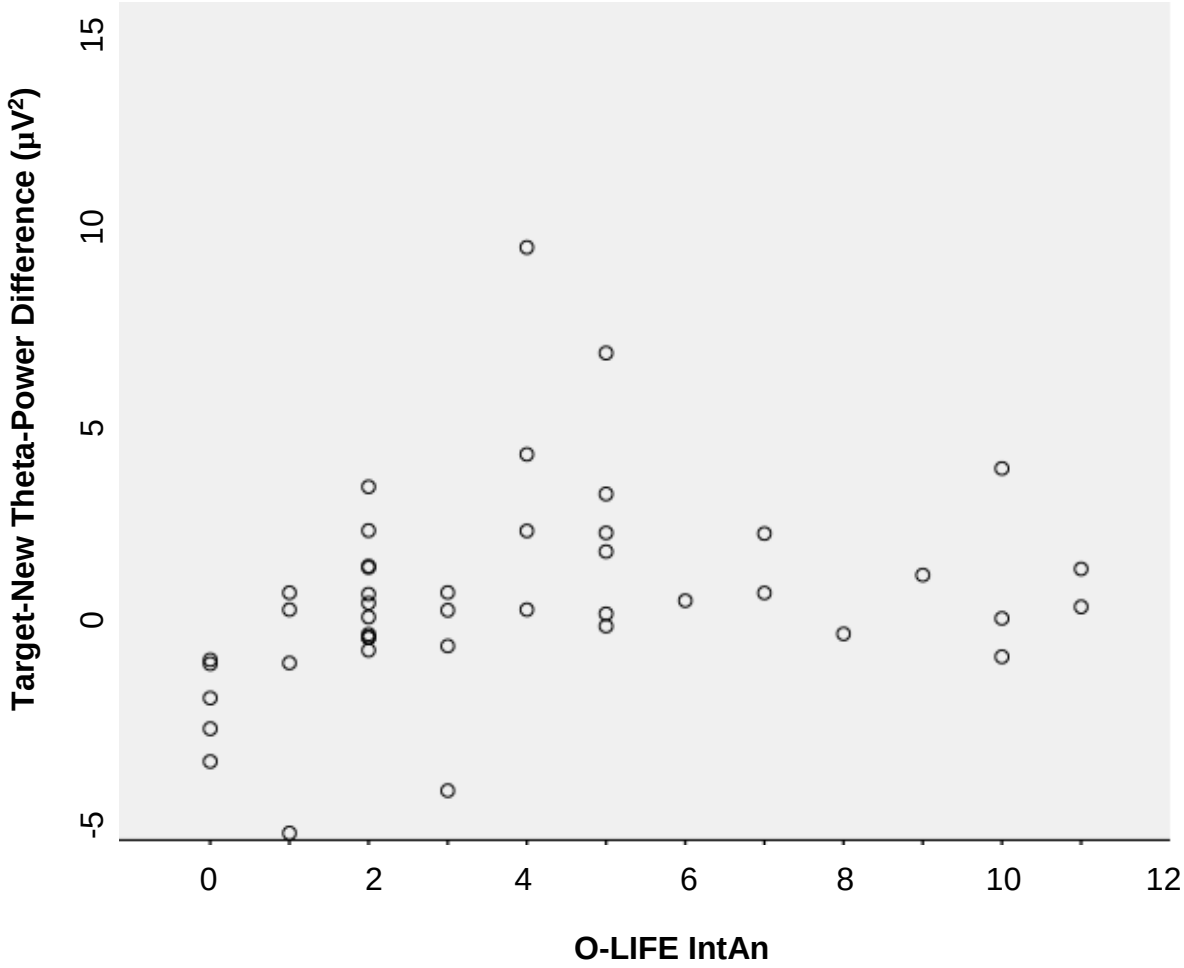

Figure 9 – Scatterplot of theta-power (μV^2) target-new differences for the imagine condition against negative schizotypy scores (O-LIFE IntAn [introvertive anhedonia]). Theta-power target-new difference measures are calculated using mean values from Fz, 600-1000ms post-stimulus presentation.

Schizotypy. Theta-power target-new difference measures and measures of positive schizotypy were entered into Spearman's correlation analyses as a first-step to investigating whether schizophrenia symptomatology is related to patterns of theta-activity. Analyses with measures of positive schizotypy, in accordance with the principal hypothesis, did not reveal any significant correlations. However, exploratory investigations using measures of negative and disorganised schizotypy revealed a significant positive correlation between target-new theta-power differences in the imagine condition and measures of

negative schizotypy ($\rho(42)=0.46, p=.002$; see Figure 9 for a scatterplot showing this relationship).

Discussion

Three hypotheses were explored in this project. In accordance with SCERT (Watrous & Ekstrom, 2014), across all hypotheses differences between conditions (imagine/perceive) were anticipated. First, it was predicted that there would be significant positive correlations between difference measures of theta-power between target and new items and measures of behavioural discrimination, as well as estimates of recollection. In relation to this, one significant positive correlation was identified between difference measures of theta-power and estimates of recollection in the imagine condition only. Second, it was anticipated that there would be positive correlations between the aforementioned difference measures of theta-power and ERP indices of recollection (the left-parietal old/new effect). However, analyses revealed one significant *negative* correlation between difference measures of theta-power in the perceive condition and target-new difference ERP measures in the imagine condition. Finally, negative correlations between measures of positive schizotypy and difference measures of theta-power were expected. These analyses did not reveal significant effects. However, exploratory correlations between other measures of schizotypy and difference measures of theta-power revealed a significant positive correlation with measures of negative schizotypy.

The absence of target-new difference measures of theta-power from 100-300ms post-stimulus presentation over Pz raises questions about the functional significance of this modulation. In ERP literature, modulations occurring within the first 100ms post-stimulus presentation are typically viewed as sensory

components that reflect the physical properties of a stimulus (Sur & Sinah, 2009). For example, the P50 component is a positive deflection in the ERP recording occurring approximately 50ms post-stimulus presentation (Adler, Pachtman, Franks, Pecevich, Waldo & Freedman, 1982). The magnitude of this effect is considered to be an index of the strength of an inhibitory pathway; the extent to which people can selectively attend to salient, and ignore redundant or repetitive stimuli (Clementz, Geyer & Braff, 1997). Johannesen, Kieffaber, O'Donnell, Shekhar, Evans and Hetrick (2005) found that the P50 effect was compromised of a low-frequency component (1-20Hz), and a gamma-band component. This low-frequency component attenuated in a manner similar to the P50 to repeated stimuli. Furthermore, this attenuation occurred to a lesser extent for people with schizophrenia compared to control participants.

The above evidence suggests the early theta-modulation observed in the present data could be related to sensory-gating processes, rather than EM processes. The differing time-course of the theta-response observed in the present findings, compared to those of Johannesen et al. (2005), is likely explained by the temporal-smearing of data that occurs with time-frequency analyses (Cohen, 2014). The lack of difference between target and new items could indicate that participants paid equal attention to both types of items; which would be anticipated in this paradigm. In light of this, the absence of a correlation between a sensory process and a later cognitive component is not necessarily surprising (Fell et al., 2004). Although, the topography of maximal effect for the P50 ERP component differs from the observed increase in theta-power in the present findings (maximal at Cz compared to Pz here; e.g. Clementz et al., 1997), this difference is unlikely to be significant. The P50 is a wide-spread effect

covering multiple electrode-locations, and as seen in Figure 3, early-theta power in the present data is similarly wide-spread. Furthermore, Johannesen et al (2005) identified that a gamma-band component also contributed to the P50 ERP effect. Consequently, differences in topography may be accounted for by the absence of activity from this frequency-band. Nonetheless, further investigations would be required to better understand relationships between this early-posterior theta-modulation and ERP components of sensory-gating, and the importance of this topography.

The presence of target-new differences over Fz from 600-1000ms indicates that these processes are more likely to be related to EM processes acting during or after retrieval. However, there are multiple processes that contribute to successful EM retrieval, and thus this raises questions about the functional significance of these differences. Johnson, Minton and Rugg (2008) advocated that using the left-parietal old/new effect as a reference point can facilitate understanding the functional significance of effects. Assuming the left-parietal old/new effect is a generic index of recollection (e.g. Donaldson & Curran, 2007; Johnson et al., 2008; MacKenzie and Donaldson, 2007), processes preceeding this time window (500-800ms) are likely to reflect processes contributing to retrieval of content. By contrast, those occurring during or after this time window could more readily be attributed to processes acting on the contents of retrieval, or post-retrieval processes (Yick & Wilding, 2008; 2014).

By this view, the time window of the present target-new differences (600-1000ms) likely reflect post-retrieval processing, rather than processes that contribute to the recovery of contents from EM. The positive correlation between the target-new difference in theta-power and the estimate of recollection in the

imagine condition however suggests this effect may index processes that relate to content-specific retrieval, namely items that have been imagined. This latter interpretation assumes that the estimate of recollection indexes processes relating the retrieval of contents only. As previously highlighted, many processes contribute to successful EM and consequently, behavioural measures alone in the absence of temporally-sensitive neuroimaging methods are limited in their ability to differentiate the separable processes contributing to successful EM outputs. Nonetheless, it is important to recognise that this correlation with behavioural performance is content specific. By considering these findings in the context of the relationships with the ERP data we are better able to differentiate these interpretations.

In ERP literature, the right-frontal old/new effect is a positive deflection in the recording from 400-1500ms post-stimulus presentation, which is more positive-going for studied compared to unstudied items (e.g. Cruse & Wilding, 2011; Senkfor & Van Petten, 1998; Wilding & Rugg, 1996), and is considered to index processes acting on the contents of retrieved information in service of task goals (Cruse & Wilding, 2009). If the magnitude of the left-parietal old/new effect indexes the amount of contextual information recovered from EM, it would be logical that when sufficient details are recovered, post-retrieval processes are engaged to a lesser extent, than when fewer details are recovered. This could explain the negative correlation observed between measures of theta-power and ERP indices of recollection across conditions of interest. The specific crossed-correlation between theta-power in the perceive condition and the left-parietal old/new effect in the imagine condition suggests that people with schizophrenia have a particular difficulty recovering and differentiating imagined content. When

sufficient contextual details are recovered during retrieval, post-retrieval processes are engaged to a lesser extent. However, when fewer contextual details are recovered and accurate source-monitoring judgements cannot be made, for namely imagined items, post-retrieval processes are engaged in service of task-performance. Since insufficient details are recovered during the initial memory search, it makes sense that when this strategy fails people will engage post-retrieval processes using alternate sources of memory, namely perceive items. In light of this, it is maybe less surprising that a specific-cross condition has been identified here.

SCERT (Watrous & Ekstrom, 2014) proposes that external signals from the environment are received via sensory receptors which establish, and become associated with, internal contexts; namely specific time- and frequency-specific patterns of neural-activity. It is important to acknowledge however that the process through which cell assemblies emerge is yet to be determined. The above mechanism proposes an external locus of initiation. Another possibility could be intrinsic brain dynamics or top-down processes (Watrous & Ekstrom, 2014). In all likelihood, both mechanisms play a role, however it is difficult to demonstrate confirmatory evidence for either at the macroscopic level in humans. Available evidence at present comes mostly from animal studies; current techniques are only just starting to explore network dynamics at each and across the levels proposed by SCERT (Watrous & Ekstrom, 2014). Although the proposed mechanisms have high face validity in light of available evidence, further work is needed to verify the mechanisms of this theory.

According to SCERT (Watrous & Ekstrom, 2014), different environmental cues are associated with specific distributions of activity. Considering the present

experimental paradigm in light of this, it was anticipated that imagined and perceived items would be associated with different distributions. This hypothesis is supported by observed differences in topography of effects by Doidge et al (2017). ERP old/new effects in the imagine condition had markedly more anterior distributions than those for the perceive condition from 500-1100ms post-stimulus presentation. Furthermore, effects from 300-500ms post-stimulus presentation were found to have a more focal-anterior distribution in the imagine condition compared to the more distributed-anterior distribution in the perceive condition. These findings indicate that content-specific processes can act both during retrieval and post-retrieval to support EM performance.

The absence of direct differences in theta-measures between conditions in the present findings do not contradict this theory. First, a data-driven approach was adopted to identify scalp locations where effects were maximal. Consequently, only limited electrode locations were entered into statistical analyses, namely Fz. Questions about content-specific processes are better addressed using broader electrode-montages as employed by Doidge et al. (2017). Second, the imagine-specific correlation between frontal-theta and estimates of recollection are in keeping with the findings of Doidge et al. (2017), where content-specific processes can act during retrieval. It is likely that due to the epoch employed, and temporal smearing of the time-frequency data that this frontal-theta modulation reflects both content-specific retrieval processes and post-retrieval processing. Considering post-retrieval processing has been implicated in memory retrieval in service of task goals (e.g. Cruse & Wilding, 2009), the present findings provide some evidence that top-down processes may contribute to the reactivation of memory networks; which could be considered

preliminary evidence to support some of the mechanisms proposed by SCERT (Watrous & Ekstrom, 2014). Further investigations specifically addressing the frontal theta-modulation and the relationship to ERP indices of recollection, post-retrieval monitoring and behavioural measures of recollection would add strength to this interpretation of the present data.

Frith (1992) proposed that one hypothesis for hallucinations for people with schizophrenia was the misattribution of internally generated events to external sources; thus positive symptoms of schizophrenia and source monitoring are intrinsically linked. In the present data, there was a positive relationship between theta-power and negative schizotypy, rather than positive schizotypy. Whilst at first sight this appears to contradict the above hypothesis, these findings still emphasise the intrinsic relationship between schizophrenia symptomatology and source monitoring. Negative rather than positive symptoms have been previously associated with cognitive deficits for people with schizophrenia in meta-analyses (Aleman et al., 1999; Nieuwenstein, Aleman, & de Haan, 2001). Thus, it is maybe less surprising that negative symptoms have been associated with theta-power in this investigation. The direction of the relationship observed may seem counter intuitive. However, increases in theta-power in service of engaging more post-retrieval processing to aid task performance may represent a strategy to compensate for EM retrieval difficulties experienced by those higher in schizotypy. Establishing whether people with schizophrenia would similarly demonstrate such compensation strategies would be an interesting direction for future research.

Confirmatory factor analyses have revealed that schizotypy has the same tripartite factor structure corresponding to the various behaviours and beliefs

required for a diagnosis of schizophrenia (Bentall, Claridge, & Slade, 1989; Mason, Claridge, & Williams, 1997). Other researchers have argued however these experiences are not necessarily qualitatively comparable to those experienced by people with schizophrenia (Lawrie, Hall, McIntosh, Owens, & Johnstone, 2010). Specifically, Lawrie et al. (2010) advocated that diagnoses are based on multidimensional factors which vary across time and contexts. By contrast, endophenotypic approaches typically focus on individual symptoms and thus have limited generality to people with schizophrenia. Nonetheless, it is important to acknowledge the advantages of such approaches. Patient studies are often resource-intensive. Thus, employing endophenotypic approaches, such as measures of schizotypy, offer a way of refining hypotheses that can subsequently be tested in patient populations (Kwapil & Barrantes-Vidal, 2015). These arguments do not undermine the need for further research to better understand the relationship between schizotypy and schizophrenia, and for investigations to understand the relevance of late-frontal theta to EM retrieval for people with schizophrenia, and negative symptomatology specifically.

As can be seen in Figure 3, changes in power extend beyond the theta-range (4-8Hz); namely into the delta- (1-4Hz) and alpha-ranges (8-12Hz). Several authors have advocated that differential activity between those with and without schizophrenia are found in frequency-ranges beyond those typically associated with EM, including alpha-activity (Basar & Guntekin, 2013; Canuet et al., 2010; Haenschel et al., 2009). Alpha-power modulations have been identified during retrieval, though this has mostly been identified when working memory tasks have been employed. More specific investigations using broader frequency-

ranges would be helpful to understand the role of alpha-power modulations to EM retrieval specifically.

Clinical Implications

Identifying that negative symptoms of schizophrenia are more implicated in EM retrieval processes, particularly those involved in the retrieval of imagined contents, has a range of clinical implications including: training, practice and service delivery.

Stahl and Buckley (2006) suggest that our healthcare system has shown a gradual bias towards the assessment and treatment of positive symptoms, rather than negative or cognitive symptoms; despite these latter symptoms being more strongly associated with functional outcomes for people with schizophrenia (e.g. Grant and Beck, 2009). The reasons for this are not clear, however Stahl and Buckley (2006) have suggested it is because these symptoms are more subtle than positive symptoms; therefore, significant others supporting those with schizophrenia may not bring these symptoms to the attention of clinicians. The current research suggests it may be of benefit for healthcare professionals to be trained to also assess negative and cognitive symptoms, and to consider approaches to treat and support these difficulties specifically.

To date, most interventions, medication and psycho-therapy, for people with schizophrenia focus on alleviating the distress caused by positive symptoms (e.g. Sharma, 1999; Steel & Smith, 2013). Even atypical medications, whilst being more effective than typical medications, are limited in their ability to remediate negative symptoms (Sharma, 1999). Taken together, this provides

evidence to suggest by improving the experience of negative symptoms, we can improve both EM difficulties and quality of life in people with schizophrenia.

There are overlaps in symptomatology between negative symptoms of schizophrenia and depression (Chaturvedi, Rao, Mathai, Sarmukaddam & Gopinath, 1985). Behavioural activiation techniques have been shown to be effective in alleviating depressive symptoms (Ekers, Webster, Van Straten, Cuijpers, Richards, & Gilbody, 2014). By this token, behavioural activation techniques are likely to be helpful in alleviating some negative symptoms for people with schizophrenia. Such approaches are in accordance with current NICE Guidelines for people with schizophrenia (NICE, 2014). Further research directly investigating the effectiveness of behavioural activation techniques for improving EM retrieval, and associated measures, for people with schizophrenia would be required to verify this, however.

Finally, knowing people with schizophrenia experience difficulties with memory could influence how services interact with such service users. Many services respond punitively towards people who do not attend appointments or do not take their medication. This and other research suggests that for people with schizophrenia such lapses have a neurobiological base and it indicates that non-compliance behaviour may not be intentional. To support people, services could implement text reminders for appointments or help people set alarm reminders for their medication. Further research would be required to ascertain if such changes improved service engagement, however.

Strengths and Limitations

The principle strength of this study was that no significant differences were identified between conditions in terms of measures of behavioural performance. Thus, any differences in theta-activity between conditions could not be attributed to differences in task performance; rather any differences identified would be indicative of content-specific neural activity. Another is the data-driven approach by which the epoch of interest was identified for calculating difference measures of theta-power for each condition of interest. Such a data driven approach prevents cyclical, or biased data-analysis strategies being employed (Cohen, pers. comm.).

There are limitations to this study. First, the experimental design employed here was not designed with time-frequency analyses in mind. However, as previously discussed it is unlikely this contributed extensively to the observed effects; especially in light of the fact this would impact conditions equally, yet content-specific effects have been observed. Second, the restricted analysis strategy employed here limits the strength of conclusions that can be drawn here. Similarly, the presence of multiple outliers limits the strength of the correlational outcomes reported here. Further case-by-case investigations to understand if there is a pattern to these outliers in comparison to the rest of the sample would be an important next step and would strengthen the findings reported here. Despite these limitations, the present findings provide important questions for future research.

Conclusion

The present results indicate that frontal theta-power is likely involved in both content-specific retrieval of imagined information, and post-retrieval processes acting in service of differentiating imagined content. Further research specifically addressing this interpretation of the present data would strengthen these conclusions. The presence of a correlation between measures of theta-power and negative schizotypy indicates alleviating these symptoms may be an important treatment target. Nonetheless, these findings raise questions about the utility of endophenotypic approaches for investigating cognition in people with schizophrenia. Further research would benefit from investigating these hypotheses directly with people with schizophrenia.

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Appendix A: Ethical Approval

CLES – Psychology
Psychology
College of Life and Environmental Sciences
University of Exeter
Washington Singer Building
Perry Road
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CLES – Psychology Ethics Committee

Dear Amie Doidge

Ethics application - eCLESPsy000053
Theta power and memory retrieval: Applications to schizotypy and schizophrenia.

Your project has been reviewed by the CLES – Psychology Ethics Committee and has received a Favourable opinion.

The Committee has made the following comments about your application:

If you have received a Favourable with conditions, Provisional or unfavourable outcome you are required to re-submit for full review and/or confirm that committee comments have been addressed before you begin your research.

If you have any further queries, please contact your Ethics Officer.

Yours sincerely

Date: 06/04/2018

CLES – Psychology Ethics Committee

Appendix B: Normality Tests

Variables were tested for normality of distribution using Shapiro-Wilk tests (Ghasemi & Zahediasl, 2012). As can be seen in Table A, very few variables were normally distributed. Box plots were produced to investigate the presence of outliers. As can be seen in Figure A, several variables are impacted by statistical outliers; outliers make up 22.7% of the data. The large percentage of data considered to be statistical outliers in conjunction with the inconsistent pattern of cases identified as outliers means it is inappropriate to apply typical methods of addressing outliers (e.g. trimming or winsorizing; Ghosh & Vogt, 2012); these are likely to be valid observations. Consequently, cases were treated as any other data-point and the implications of outliers were taken into consideration when interpreting the data. As assumptions of normality were violated, non-parametric Spearman's correlations were conducted; non-normality can inflate type I error rates and reduce power in Pearson's r correlations (Bishara & Hittner, 2012). When assumptions of normality are violated Spearman's, compared to Pearson's r correlations, are better powered; rank-ordering reducing the impact of outliers (Fowler, 1987). ANOVAs and t-tests were still conducted; both tests are considered robust to violations of normality (Erceg-Hurn & Mirosevich, 2008).

Table A. Outcomes from Shapiro-Wilk tests for normality.

Variable	Statistic	Significance
PCorr[target|new] Imagine	0.96	0.178
PCorr[target|new] Perceive	0.94	0.031
R Imagine	0.92	0.005
R Perceive	0.92	0.004
Fz Theta-power 600-1000ms Imagine	0.92	0.006
Fz Theta-Power 600-1000ms Perceive	0.95	0.040
Left-Parietal Old/New Effect Imagine	0.98	0.459
Left-Parietal Old/New Effect Perceive	0.98	0.766

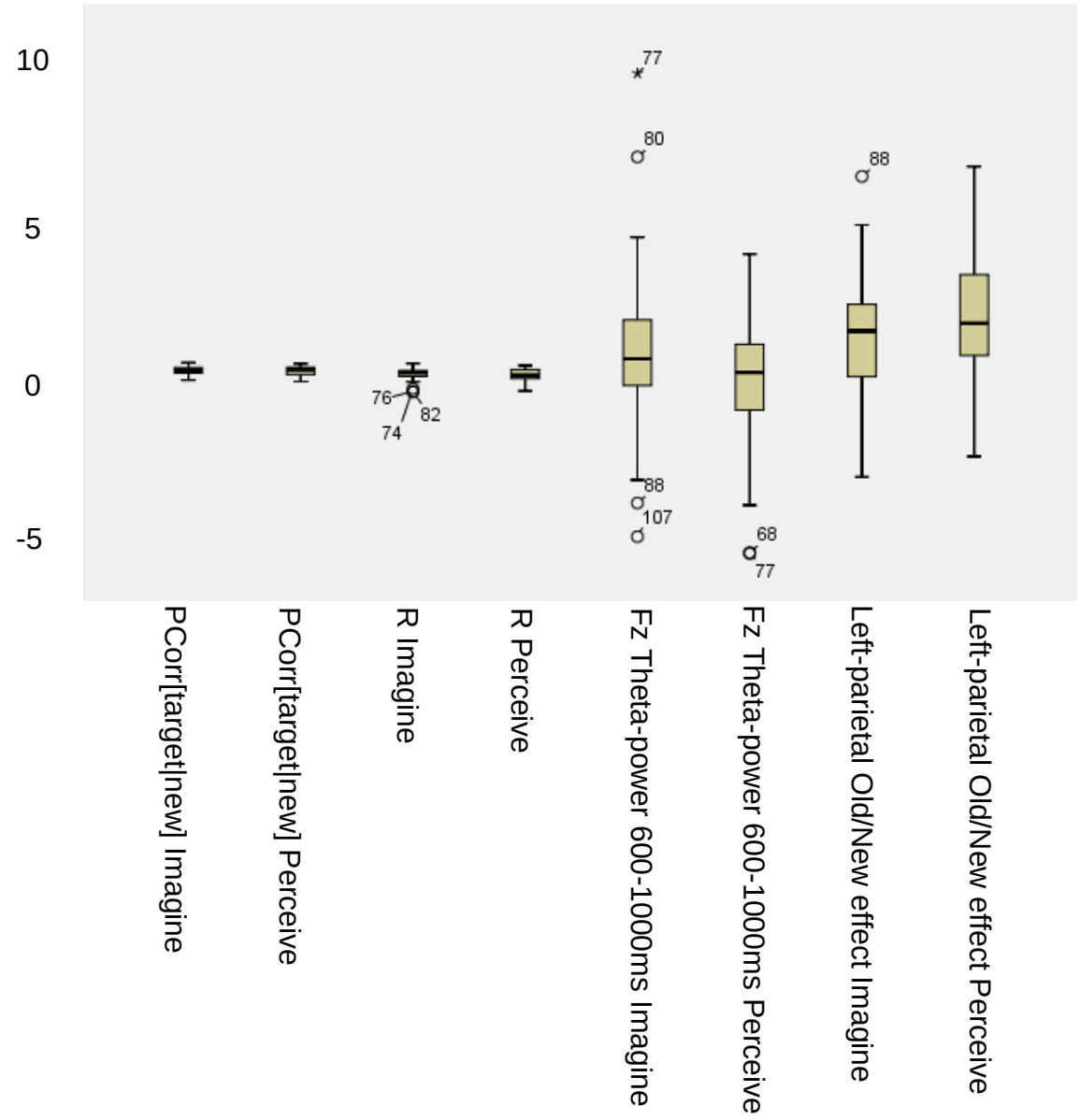

Figure A: Box plots showing the median and inter-quartile ranges for variables included in statistical analyses. Outliers are highlighted by circles and astericks. Numbers represent the case numbers the data point corresponds to.

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Appendix C: Dissemination Statement

Dissemination of results will take place at multiple levels. First, a research presentation to disseminate findings to colleagues and other professionals has been scheduled to take place at the University of Exeter in June 2018. Second, revised versions of the literature review and the empirical paper will be submitted to journals for publications: initial target journals have been identified as Psychological Bulletin and the Journal of Abnormal Psychology respectively. Finally, revised outcomes from the empirical paper will be submitted for presentation at professional conferences (e.g. Society for Biological Psychiatry, May 16-18th 2019).

Unfortunately, as the data was collected in 2013, contact details for participants who took part in this study are no longer available. Consequently, it is not possible to send a summary of these outcomes to participants directly.

Appendix D: Instructions for Contributors of Journal of Abnormal Psychology

Scope of the Journal

The Journal of Abnormal Psychology® publishes articles on basic research and theory in the broad field of psychopathology and other abnormal behaviours, their determinants, and correlates.

The following topics fall within the journal's major areas of focus:

- psychopathology — its etiology, development, symptomatology, and course
- normal processes in abnormal individuals
- pathological or atypical features of the behavior of normal persons
- experimental studies, with human or animal subjects, relating to disordered emotional behavior or pathology
- sociocultural effects on pathological processes, including the influence of gender and ethnicity
- novel methods developed to measure psychopathological mechanisms

Empirical papers with a strong theoretical framework and/or models of computational parameters are particularly encouraged. Theoretical papers of scholarly substance on abnormality may be appropriate if they advance understanding of a specific issue directly relevant to abnormal psychology and fall within the length restrictions of a regular (not extended) article. Case Studies from either a clinical setting or a laboratory will be considered if they raise or illustrate important questions that go beyond the single case and have heuristic value.

Each article should represent a significant addition to knowledge and understanding of abnormal behaviour in its aetiology, description, or development. Visit the Sample Articles page to read published articles.

In order to improve the use of journal resources, it has been agreed that the Journal of Abnormal Psychology will not consider articles dealing with the diagnosis or treatment of abnormal behavior, and the Journal of Consulting and Clinical Psychology will not consider articles dealing with the aetiology or descriptive pathology of abnormal behaviour.

Therefore, a study that focuses primarily on treatment efficacy should be submitted to the Journal of Consulting and Clinical Psychology. However, a longitudinal study focusing on developmental influences or origins of abnormal behaviour should be submitted to the Journal of Abnormal Psychology.

Submission

Submit manuscripts electronically through the Manuscript Submission Portal. All efforts should be undertaken to submit manuscripts electronically to the editor. Files can be sent in Microsoft Word, or as a PDF file. The version sent should be consistent with the complete APA-style printed version.

Dolores Albarracín, Editor
Department of Psychology
University of Illinois at Urbana Champaign
603 E. Daniel St.
Champaign, IL 61801

General correspondence may be directed to the Editor's Office.

In addition to addresses and phone numbers, please supply electronic mail addresses and fax numbers, if available, for potential use by the Editorial

Office and later by the Production Office. Keep a copy of the manuscript to guard against loss. Psychological Bulletin is now using a software system to screen submitted content for similarity with other published content. The system compares the initial version of each submitted manuscript against a database of 40+ million scholarly documents, as well as content appearing on the open web. This allows APA to check submissions for potential overlap with material previously published in scholarly journals (e.g., lifted or republished material).

Masked Review Policy

The identities of authors will be withheld from reviewers and will be revealed after determining the final disposition of the manuscript only upon request and with the permission of the authors. Authors are responsible for the preparation of manuscripts to permit masked review. Manuscripts submitted electronically should include all author names and affiliations, as well as the corresponding author's and co-authors' contact information, in the box labelled "cover letter," not in the manuscript file. Every effort should be made to ensure that the manuscript itself contains no clues to the authors' identities, including deletion of easily identified self-references from the reference list. If an author feels that revealing his or her identity is critical to receiving a fair review, such a request along with its justification should be made in the cover letter accompanying the manuscript. Please ensure that the final version for production includes a by-line and full author note for typesetting.

Manuscript Preparation

Prepare manuscripts according to the Publication Manual of the American Psychological Association (6th edition). Manuscripts may be copyedited for bias-

free language (see Chapter 3 of the Publication Manual). Review APA's Checklist for Manuscript Submission before submitting your article. Double-space all copy. Other formatting instructions, as well as instructions on preparing tables, figures, references, metrics, and abstracts, appear in the Manual. Additional guidance on APA Style is available on the APA Style website. Below are additional instructions regarding the preparation of display equations, computer code, and tables.

Display Equations

We strongly encourage you to use MathType (third-party software) or Equation Editor 3.0 (built into pre-2007 versions of Word) to construct your equations, rather than the equation support that is built into Word 2007 and Word 2010. Equations composed with the built-in Word 2007/Word 2010 equation support are converted to low-resolution graphics when they enter the production process and must be rekeyed by the typesetter, which may introduce errors.

To construct your equations with MathType or Equation Editor 3.0:

4. Go to the Text section of the Insert tab and select Object. Select MathType or Equation Editor 3.0 in the drop-down menu.
5. If you have an equation that has already been produced using Microsoft Word 2007 or 2010 and you have access to the full version of MathType 6.5 or later, you can convert this equation to MathType by clicking on MathType Insert Equation. Copy the equation from Microsoft Word and paste it into the MathType box. Verify that your equation is correct, click File, and then click Update. Your equation has now been inserted into your Word file as a MathType Equation.

6. Use Equation Editor 3.0 or MathType only for equations or for formulas that cannot be produced as Word text using the Times or Symbol font.

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Because altering computer code in any way (e.g., indents, line spacing, line breaks, page breaks) during the typesetting process could alter its meaning, we treat computer code differently from the rest of your article in our production process. To that end, we request separate files for computer code.

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Tables

Use Word's Insert Table function when you create tables. Using spaces or tabs in your table will create problems when the table is typeset and may result in errors.

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Authors submitting manuscripts to Psychological Bulletin are required to provide two to three brief sentences regarding the relevance or public health significance of the study or meta-analysis described in their manuscript. This description should be included within the manuscript on the abstract/keywords page. It should be written in language that is easily understood by both professionals and members of the lay public.

Examples:

"This meta-analysis strongly suggests that (description of a given psychosocial treatment) is an effective treatment for anxiety, but only if it is of mild to moderate severity. For persons with severe anxiety, additional treatments may be necessary."

"This systematic review indicates that personality changes following psychotherapy and pharmacotherapy. The changes are small and persist for (description of time in months or years)"

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To be maximally useful, these statements of public significance should not simply be sentences lifted directly from the manuscript. This statement supports efforts to increase dissemination and usage of research findings by larger and more diverse audiences. In addition, they should be able to be translated into

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