Using the Concept of Complexity to Guide Translational Research in Psychiatry: from Electroencephalography to Mental Health Services Development

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Abstract

The presented work unites several distinct lines of research, asserting that the broader construct of *complexity* (with its various connotations) may be uniquely relevant and informative to our understanding and management of psychotic disorders.

Part 1 outlines the candidate's contributions to the development of EEG methodology in clinical populations in an effort to most directly capture *neural noise* and *complexity*. The advent of oscillatory analysis facilitated the study of ongoing background activity of the EEG. Further exploration of this background activity demonstrated that increased neural noise (as quantified by Lempel-Ziv complexity) is highly correlated with, and conceptually very relevant to, positive symptoms of psychosis. Part 2 describes how considering the complexity of clinical psychosis states justifies the use of human laboratory studies using psychotomimetic drugs such as tetrahydrocannabinol and ketamine. Part 3 explains how the ideas and inferences from the work in Parts 1 and 2 can inform the *environment* of psychotic disorders, specifically the candidate's work in prescribing practices and first episode psychosis service design.

The thesis concludes that EEG studies of clinical populations face particular methodological challenges, however the resultant technical advancements have expanded our view of neural function to the particular benefit of our understanding of psychosis. EEG measures of complexity may be amongst the most sensitive biomarkers associated with positive symptoms, however more empirical research is called for to confirm this observation. Human laboratory studies of psychotomimetic drugs in healthy humans may continue to prove useful, in circumventing the phenomenological and patho-etiological complexity of clinically occurring psychosis. As a next step, multi-modal studies (combining biophysical signals, individual phenomenology and even population level outcomes) in combination with data mining techniques might further characterize the complexity within psychosis. Psychotic disorders, as complex problems, warrant framing and intervention informed by complexity.

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Tables

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Preface

The following body of work and related commentary is humbly submitted for the award of PhD by Publication. It represents a synopsis of a singular line of scientific enquiry (albeit, but vitally, spanning a diverse range of techniques and fields) - using the notion of *complexity* as a core concept to guide translational research in psychiatry (and more specifically psychosis) through developing new research methodologies and clinical approaches more attuned to this orientation.

The selected publications represent a pragmatic program of research, by a clinical academic, leveraging opportunities to collaborate across diverse fields and modes of investigation, in order to apply translational concepts in ways not otherwise possible. When not primary author, the candidate has made specific and substantive intellectual contributions to the work, derived from and germane to the unifying thesis presented here. This body of work and associated research training and experience (including completion of core didactics and coursework for the PhD program at the University of Nottingham, UK and completion of 3 years clinical research fellowship in psychotic disorders at Yale University, USA) has been used to support and inspire the candidate's current work as an independent researcher (Assistant Professor at Yale University): 2 ongoing research grants, international presentations, a textbook in preparation, 2 course directorships and other submitted manuscripts. This ongoing work and other possible future directions will also be discussed.

WORK	TITLE	AUTHORSHIP	% CONTRIBUTION
PEER-REVIEWED WORKS			
1	*Electrophysiological indices of abnormal error-processing in adolescents with attention deficit hyperactivity disorder (ADHD)*	Second (of seven)	35
2	*Psychotomimetic and Cognitive Effects of Delta^9-Tetrahydrocannabinol in Laboratory Settings*	First (of six)	45
3	*The psychosis-like effects of Δ 9-tetrahydrocannabinol are associated with increased cortical noise in healthy humans*	Second (of ten)	30
4	*Testing differences in the activity of event-related potential sources: important implications for clinical researchers*	Second (of six)	45

5	*The Endocannabinoid System and Schizophrenia: Links to the Underlying Pathophysiology and to Novel Treatment Approaches*	Co-first (of four)	45
6	*A Prescription for "Deprescribing" in Psychiatry*	Co-first (of two)	50
7	*Psychopharmacology Prescribing Workshops: A Novel Method for Teaching Psychiatry Residents How to Talk to Patients About Medications*	Second (of twelve)	28
8	*Building Early Intervention Services for Psychotic Disorders: A Primer for Early Adopters in the US*	Second (of three)	35
NON PEER-REVIEWED *SUPPLEMENTARY* WORKS			
S1	*Impaired synchronization of neural oscillations immediately following auditory stimuli represents a pervasive deficit in brain recruitment in schizophrenia*	First (of five)	80
S2	*Pre-stimulus theta power predicts the suppression of beta synchronization during motor response: Does a disrupted effect in schizophrenia reflect pathological baseline theta activity?*	First (of five)	80
S3	*Cannabinoids Generate Neural Noise in Humans: A Nonlinear Analysis of EEG Signals*	Second (of eleven)	30
S4	*Ketamine and depression*	First (of one)	100
Total % contributions			**603**

Table 1. Summary of works with percent contributions (per joint authorship declarations)

Complex systems and problems

The etymology of the word 'complexity' draws from the Latin *complexus* – meaning 'together' and *plectere,* 'to weave' or 'braid'. Therefore the more entwined, connecting parts within a system, the more complex it is. Individual parts exhibit different properties when viewed in isolation than in the context of the whole system, and dramatic unpredictable changes may result from seemingly minor changes in the system's environment. Real world systems demonstrating complexity, such as weather systems and the brain are often referred to as *complex adaptive system*s [2].

Complex systems are *non-linear* and produce high degrees of *noise, tension* and *fluctuation* in their interaction with the environment [3]. By virtue of manifesting *nonlinear feedback,* they allow for *emergence*, *self-organization, adaptation* and *learning* [4]. Non-linear feedback in complex systems is facilitated by the presence of multiple interacting feedback loops, making the output difficult to predict and control [4]. Their outcomes can be probabilistic, uncertain

and non-predictable, and *emergence* can also occur. *Emergence* is the appearance of novel phenomena (on a macro-level) resulting from self-organization of a complex system [5].

Complex systems may manifest complex problems. In conceptualizing approaches to health care reform, Glouberman and Zimmerman illustrated the distinction between a simple, complicated and complex problem [3] (see Table 2). Simple problems, when mastered, yield easily predictable outcomes. Complicated problems are comprised of multiple interconnected elements, at large scale, but can be predicted once understood. Whereas complex problems possess both simple and complicated components, with added *sensitivity to context*, *interdependency, adaptation* and *non-linearity* [3]. Therefore, complex problems, due to their nature, must be addressed as entire systems, to be *influenced* and not *controlled* [6].

Approaching Simple, Complicated versus Complex Problems		
Simple: *Following a Recipe*	**Complicated: *Sending a Rocket to the Moon***	**Complex: *Raising a Child***
The recipe is essential	Formulae are critical and necessary	Formulae have a limited application
Recipes are tested to assure easy replication	Sending one rocket increases assurance that the next will be OK	Raising one child provides experience but no assurance of success with the next
No particular expertise is required. But cooking expertise increases success rate	High levels of expertise in a variety of fields are necessary for success	Expertise can contribute but is neither necessary nor sufficient to assure success
Recipes produce standardized products	Rockets are similar in critical ways	Every child is unique and must be understood as an individual
The best recipes give good results every time	There is a high degree of certainty of outcome	Uncertainty of outcome remains
Optimistic approach to problem possible	Optimistic approach to problem possible	Optimistic approach to problem possible

Table 2. Comparing simple, complicated and complex problems. Adapted from [3]

Psychosis as the prototypic 'complex problem' in psychiatry

Per the American Psychiatric Association's *Diagnostic and statistical manual of mental disorders, schizophrenia spectrum and other psychotic disorders* span schizophrenia, other psychotic disorders, and schizotypal (personality) disorder and are defined by abnormalities in one or more of the five domains: delusions (fixed, false beliefs, held in the face of contradictory evidence), hallucinations (perceptions in the absence of an external stimulus), disorganized thinking, grossly disorganized or abnormal motor behavior (including catatonia),

and negative symptoms [7]. *Disorganized thinking* or *formal thought disorder* refers to abnormal connections and flow between thoughts. The individual may flit from one topic to another (*loose associations*), respond obliquely (*tangentiality*) or talk around a topic (circumstantiality). *Motor behavior may also be disorganized,* ranging from fatuousness to unpredictable agitation. *Negative symptoms of psychosis*, most prominent in schizophrenia, account for a substantial portion of the morbidity of the disorder. They include *diminished emotional expression*, *avolition* (decreased self-initiated purposeful activities), alogia (diminished speech output), anhedonia (decreased derived pleasure), and asociality (lack of interest in social interactions) [8].

Psychosis can be experienced as acute and transient, chronic and persistent, or relapsing and remitting, and can rise to the level of a disorder - generally defined by the level of resultant distress and dysfunction. In this work, schizophrenia will be accepted as the prototypic, chronic primary psychotic disorder. Beyond schizophrenia however, psychosis and psychosis-like experiences can complicate a wide range of mental and physical illnesses (such as mood disorders and delirium), as well as drug use (e.g. cannabis) but are also prevalent in approximately 7% of the general population - perhaps representing a transdiagnostic and extended phenotype [9].

Following decades of study, schizophrenia has been associated with a broad array of deficits and despite valiant efforts, eludes a widely accepted, unifying pathophysiology [10, 11]. Congruently, it has been described as a 'complex disorder' [12]. Complexity is likely relevant to all mental illness by virtue of the fact that the brain is a complex adaptive system, but specifically, an increase in the level of complexity (either via a mal-coordination of interacting elements or the additional of noisy or aberrant processes) may be hypothesized in psychosis. Of the properties of a complex system outlined above it may be that their *non-predicable outcomes, noise* and *emergent phenomena* may be most relevant to psychotic phenomena. Within this view, disorganized thinking and behavior may be framed in terms of non-predictability and noise, whereas hallucinations and delusions may be conceived as (pathological, not physiological) emergent phenomena of the brain.

In order to frame what follows, figure 1 proposes a multi-level, pluralistic view of psychosis as a disorder affecting expanding layers of function from neurons, to the individual person, to social systems. It offers both domains of functional impairment and specific examples of abnormalities observed, proposing the potential for a common principle (complexity) being relevant across all levels of the disorder.

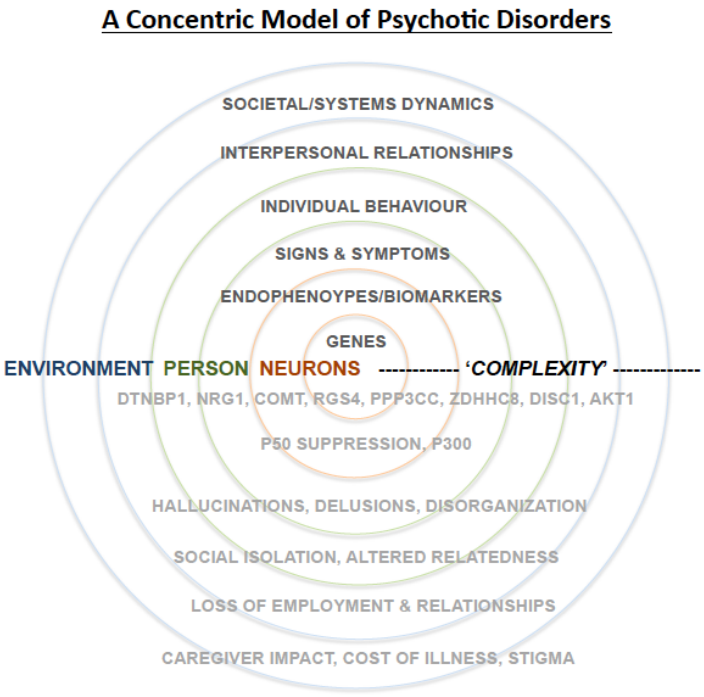

Figure 1. A concentric, multi-layer model of observations associated with psychotic disorders, proposing complexity as a common principle

In this way psychosis aligns well the idea of 'translational research'. Although first appearing in the medical literature in 1993, this term only really became in vogue in the 2000s with growing interest in connecting basic science with clinical and population based research [13]. Rather than being unidirectional however, it has more recently been conceived as a "multidirectional integration of basic research, patient-oriented research and population based research with the long-term aim of improving the health of the public" [13].

Aims

Tandon et al. 2002, observed that our conceptualization of schizophrenia has evolved alongside the techniques available to study it [11]. Similarly, the overarching aim of this body of work was to advance research methodology to better study psychiatric populations (but more specifically psychotic disorders) with the general hypothesis that *increased complexity* is a core feature that pervades all levels of these disorders and has profound relevance for their management. The published work will be presented, largely chronologically, however many ideas evolved in parallel, reflecting a multidirectional approach to translational research. The aim is also to demonstrate the candidate's diverse, yet connected contributions to research methodology, pathophysiology, clinical practice and pedagogy relevant to this thesis.

Part 1 reviews the candidate's contributions to the development of EEG methodology in

clinical populations towards tapping into the brain's complexity. The opportunity to perform secondary oscillatory analyses of event related potential EEG paradigms launched the exploration of resting state, pre-stimulus and non-stimulus-locked activity and finally neural noise measures. Increased neural noise (as quantified by Lempel-Ziv complexity) observable in psychosis states is also conceptually echoed in the phenomenology of the clinical syndromes. Part 2 exams the relevance of complexity to the study of psychosis states on the level of *the person.* Safe and rigorous research methodology is necessary towards understanding the clinical syndrome and advancing its management. Appreciating and adapting to the complex nature of psychosis can inform research approaches. Specifically, human laboratory studies using psychotomimetic drugs (in contrast to clinical psychosis) may offer a more controlled way of exploring this syndrome. Part 3 explicates how the ideas and inferences from the work in Parts 1 and 2 may be extrapolated to inform the *environment* of psychotic disorders - approaches to clinical care, (both on an individual patient and population level) as well as clinical education.

PART 1) NEURONS: Advancing EEG methods for clinical research in psychiatry

1.1 Overview of published works

- **SUPPLEMENTARY WORK S1.** *Impaired synchronization of neural oscillations immediately following auditory stimuli represents a pervasive deficit in brain recruitment in schizophrenia* [1]
  - **Contribution to the work**: generated hypothesis, designed and conducted analysis and independently wrote manuscript

- **SUPPLEMENTARY WORK S2.** *Pre-stimulus theta power predicts the suppression of beta synchronization during motor response: Does a disrupted effect in schizophrenia reflect pathological baseline theta activity?* [14]
  - **Contribution**: generated hypothesis, designed and conducted analysis and independently wrote manuscript

- **WORK 1:** *Electrophysiological indices of abnormal error-processing in adolescents with attention deficit hyperactivity disorder (ADHD)* [15]
  - **Contribution:** introduced the novel measure of inter-trial coherence (ITC) to the group, hypothesizing that it would be more sensitive than existing ERPs, participated in data collection, designed and conducted EEG data analysis, participated in preparation of manuscript

- **SUPPLEMENTARY WORK S3:** *Cannabinoids Generate Neural Noise in Humans: A Nonlinear Analysis of EEG Signals.* [16]
  - **Contribution:** significant contribution to the hypothesis, design and conduct of the EEG analysis and interpretation of the results, contributed to preparation of the manuscript

1.2 Commentary

Bioelectrical potentials are routinely measured throughout medicine to diagnose and study disease. The flow of ion-based currents generated around the selectively permeable membranes of excitable tissues generate the electromyogram (EMG), electrocardiogram (ECG) and electroencephalogram (EEG). The EEG was first reported in 1875 by Richard Caton who noted electrical oscillations on the exposed cortex of animals. The first description of human EEG was offered by psychiatrist Hans Berger in 1929 [17]. It captures perturbations in voltage at the scalp caused by net local field potentials generated in dendrites of cortical pyramidal cells (summated inhibitory and excitatory post synaptic potentials). It offers a high

temporal resolution, which aligns well with the timescale of perception [18] and cognition [19], and therefore is an ideal technique with which to explore the underlying psychophysiology of psychosis – most directly, abnormalities in those same domains: perception (e.g. hallucinations) and cognition (e.g. thought disorder).

ERPs are stereotyped transient changes in the EEG associated with an external or internal event [20]. They have been widely studied since the 1960s, are elicited through a battery of experimental paradigms and thought to reflect specific sensory or cognitive processes. The history of studies conducted in psychiatric populations includes ERP responses to conflicting information, attention and memory [21-24]. ERP components are characterised on the basis of functional context [25], amplitude, time course and scalp topography and inferred anatomical origins [26].

ERPs can in fact represent the summation of many neurological processes overlapping in time and space, which do not necessarily originate in the area of cortex directly beneath the scalp topography of the ERP. However, if regarded as epiphenomena, meaningful interpretations may be made from ERPs, without full knowledge of the neural basis of each waveform. They hence can lend themselves to the arbitrary comparison of patient and control populations – where the functional significance underlying the ERP is inferred through the context of the experimental manipulation [17, 27].

ERP paradigms generally involve the repeated presentation of a stimulus, which, subject to experimental conditions, elicits characteristic responses. These components emerge from the ongoing EEG activity when epochs, defined around onset time of the event of interest, are averaged across stimulus presentations (or trials). This increases the signal to noise ratio of the activity consistent in time course across trials (through constructive and destructive interference – see Figure 2) hence the resultant ERP represents stimulus-locked activity. As signal to noise ratio improves with an increasing number of trials averaged, the number of available trials may bias ERP analyses, especially when dealing with smaller amplitude phenomena or subtle group differences. For example, it is suggested that the P3 ERP requires 30-60 trials, the N1 150-200 and the P1, 400-800 in order to adequately detect and study [17]. Achieving this in psychiatric populations can be challenging for a couple of reasons. Lengthy paradigms can be grueling for subjects, potentially deterring participation and affecting task performance. Secondly data may be lost due to common sources of artifact (such as movement and skin potentials), which may be greater due to underlying illness or treatment (e.g. hyperactivity of ADHD or extrapyramidal side effects caused by neuroleptic medications).

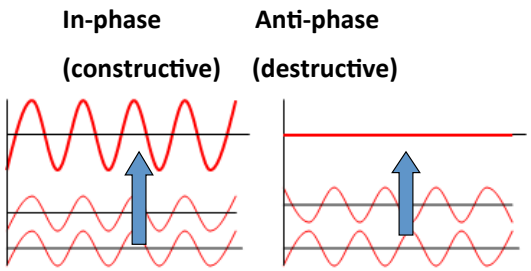

Figure 2. An illustration of the two types of interference: constructive and destructive. Oscillations in-phase summate; whereas those 180 degrees out of phase ('anti-phase') cancel out.

Given the above challenges and limitations of ERP-based studies in clinical populations, the establishment of novel EEG methodology for psychiatric populations (in order to capitalize on hard-earned and donated data) became a significant early focus of the candidate's work. This was towards two general goals: 1) to better illuminate the pathophysiology of psychosis with more proximate and/or functionally meaningful measurements and 2) to yield biomarkers to aid detection, prediction and monitoring of deficits.

1.2.1. Oscillatory analysis reveals previously undetectable deficits in neural recruitment in schizophrenia (Supplementary Work S1)

"Impaired synchronization of neural oscillations immediately following auditory stimuli represents a pervasive deficit in brain recruitment in schizophrenia" [1] [Please see Appendix 1]

Observing that the majority of EEG studies in psychiatry involved ERP analyses, the candidate was reminded that when Hans Berger first studied human in EEG in 1929, the initial phenomenon described was an oscillation (alpha wave) [17]. Around the time of the Works of this Part, spectral or oscillatory analysis (opening up a new dimension into the EEG) was starting to burgeon in clinical research, but ERP studies still dominated – offering the more established candidate biomarkers [15]. Oscillatory analysis is based on the parsimonious assumption that the EEG is derived from the summation of multiple neural oscillators and can be entirely decomposed into a spectrum of simple oscillations/sine waves (see Fourier Theorem - [28]). Fourier analysis and other more novel methods (e.g. wavelet and Hilbert transforms) all yield values for both amplitude and phase angle for a given frequency at a given time point (or rather window) - this is conventionally expressed as a single complex number [29].

Perhaps more proximate and physiologically-meaningful than ERPs, oscillations are thought to represent the rhythmic changes in local field potentials at specific frequencies, dependent on the anatomical and physiological properties of the generating networks [30-33]. The full

frequency spectrum of human EEG is conventionally divided in the following bands: delta (0-4Hz), theta (4-7Hz), alpha (8-12Hz), beta (12-30Hz) and gamma (30-100Hz). The strength of the signal at the scalp implies a degree of synchronisation between multiple neural generators, which may serve to recruit covert, behaviourally relevant networks. Functionally, oscillations of different frequencies could theoretically provide a dynamic medium of communication across a wide range of temporal resolutions. More specifically, theta and gamma have been proposed as a fundamental property of cortical circuits, used to 'code' cognition [34]. Higher frequency beta and gamma oscillations have been associated with local communication and cognitive events, whereas lower frequencies, more commonly, with longer distance communication and top-down modulation [35-37].

The 'classical model' for the generation of ERPs, describes a stimulus locked phasic signal, which occurs on top of relatively unaltered background EEG as the brain mobilizes to the incoming stimulus. Alternatively, the 'oscillatory model' is based on the concept of interference of ongoing oscillations - where the stimulus imposes a transient, non-random distribution of phase angles resulting in *interference* to produce a burst of amplitude perturbation in the EEG [38, 39]. This resetting of phase of pre-stimulus oscillations may contribute to the generation of an ERP, without requiring actual amplitude perturbation of these oscillations [40]. This revealed a previously un-tapped dimension of EEG data. Novel spectral analysis techniques meant raw datasets from established ERP paradigms could be further mined for new effects through secondary analysis (Figure 3). Oscillatory analysis demonstrated abnormalities in schizophrenia during both resting state and the processing of information [30]. These relatively new methodological advances (at the time) were leveraged in this Part's Works for the study of clinical populations.

Neural oscillations observed in the EEG had gained support in their potential role in brain recruitment [41]. Schizophrenia, with its clinical heterogeneity and varied biological abnormalities may have a fundamental impairment of neural recruitment at its core [30, 31, 42]. Psychosis may be regarded as a syndrome of network dysfunction [30, 43-45]. Documented abnormalities in glutamate, GABA, dopamine and endocannabinoid systems converge around the 'cortical microcolumns' – functional units comprised of cortical pyramidal neurons (and their associated interneurons), which generate the ongoing EEG signal [45]. Winterer et al. demonstrated an increased broadband pre-frontal 'noise' in an oddball task in schizophrenia which was negatively related to P300 amplitude and behavioural performance [46, 47]. 'Noise' was defined here as the ongoing non stimulus-locked power during the task. He introduces the idea that patients do not merely fail to activate the cortex, but fail to integrate processes in a task-related, frequency specific manner. Instead of generating a stimulus phase-related 'signal', they develop task irrelevant 'noise', perhaps as an aberration of a stochastic resonance effect (where noise and performance show an inverted 'U'

relationship) [46]. In other words, patients' ongoing neural activity may be disordered in such a way as to undermine a normal event-related response. In general, time-locked responses (i.e. ERP and evoked spectral activity measures) are diminished in schizophrenia. This may be related to increased levels of random variation of electrophysiological responses in the context of time-locked-response paradigms [47-50]. As proposed by Winterer and Weinberger, neural noise reflects the inability of neural circuits to suppress spontaneous background firing while enhancing time-locked stimulus-evoked coordinated activity [51]. Drawing from their further findings in siblings and genetic analysis, Winterer further proposed that this increased broadband noise is a potential trait marker/endophenotype for schizophrenia [47, 52].

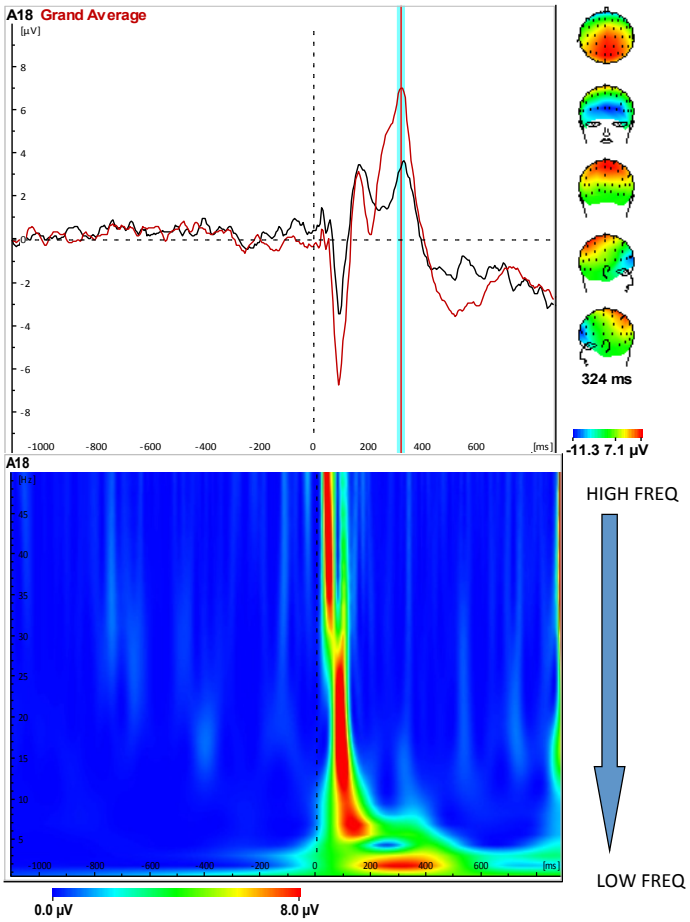

Figure 3: An illustration of a spectral decomposition of the P300 ERP. Top panel depicts classic ERP signal (voltage/time) for patients with schizophrenia (black line) vs controls (red line) at Pz. Scalp map depicts spatial distribution of activity at peak (vertical blue line). Bottom panel depicts a 3 dimension 'scalogram' for the same signal time course - both groups combined. Y-axis is frequency (Hz), x is time in milliseconds and color denotes amplitude per the scale (previously unpublished data derived from dataset yielding Works S1 and S2)

In the Works of Part 1 spectral decomposition was performed using discrete windowed Fourier transforms. *Evoked (or direct) power* was derived by first averaging the raw EEG across trials and then taking squared spectral estimates. Evoked power reflects stimulus locked activity and is expressed as an absolute power value. *Total power* was estimated by the spectral decomposition of individual trials before averaging across them - it reflects all activity. *Induced (or indirect) power* was calculated by subtracting the stimulus locked signal (across trials) from the activity at each trial, having undergone spectral decomposition and then averaging across trials - it reflects non-stimulus locked activity. Both total and induced power were considered most meaningfully expressed as a percent change from pre-stimulus baseline (akin to Event Related Synchronisation (ERS) [53]). Evoked/induced ratio was calculated as the evoked power divided by the percentage change in induced power. *Inter-trial phase coherence* (ITC) was calculated according to [54, 55] as a spectral measure developed to capture trial-by-trial variability. ITC quantifies the consistency of phase alignment across trials and is related to the 'Phase Locking Factor' described by Lachaux [38, 56]. In brief, it quantifies the extent of the distribution of phase angles in a given frequency across trials, giving values of 0 to 1 at each time point (where 0 represents completely randomly distributed phase angles between all trials and 1, identical phase at all trials). As such, ITC is independent of amplitude [54, 55]. As with ERPs, an incoming stimulus may 'recruit' the brain via the generation (or enhancement) of oscillations either phase-locked to stimulus onset of endogenously generated phase – both these processes, however are likely to occur. Therefore, the magnitude of evoked activity (defined above - where averaging occurs across trials) may be affected by not only the amplitude of the phase locked signal at each trial, but the *consistency* of the phase-relationship to stimulus onset across trials.

At the time of Work S1, decreased ITC had just been demonstrated in schizophrenia using the 40Hz 'steady state' auditory stimulation paradigm – a task designed to recruit a stereotyped cortical response [57]. Hypothesizing a even more fundamental deficit in basic neural recruitment in schizophrenia, in Work S1, the candidate proposed that this recruitment deficit might also be found during the initial pan-spectral oscillatory burst underlying the early ERP components (including N100 and extending into the latency of the P300), which was not well described at the time (see Figure 3). This burst of activity follows any attended stimulus and is likely related to sensory encoding and early recruitment [53, 58]. Work S1 was the first study to hypothesise and demonstrate a relative deficit in this initial, pan-spectral neural recruiting response in patients with schizophrenia in response to simple attended auditory stimuli (common tone of P300 paradigm). This deficit was manifest in a range of stimulus phase- and non phase-locked measures. The effect is most marked in the ratio of evoked to induced power, framed in this Work as *signal/noise ratio* [1].

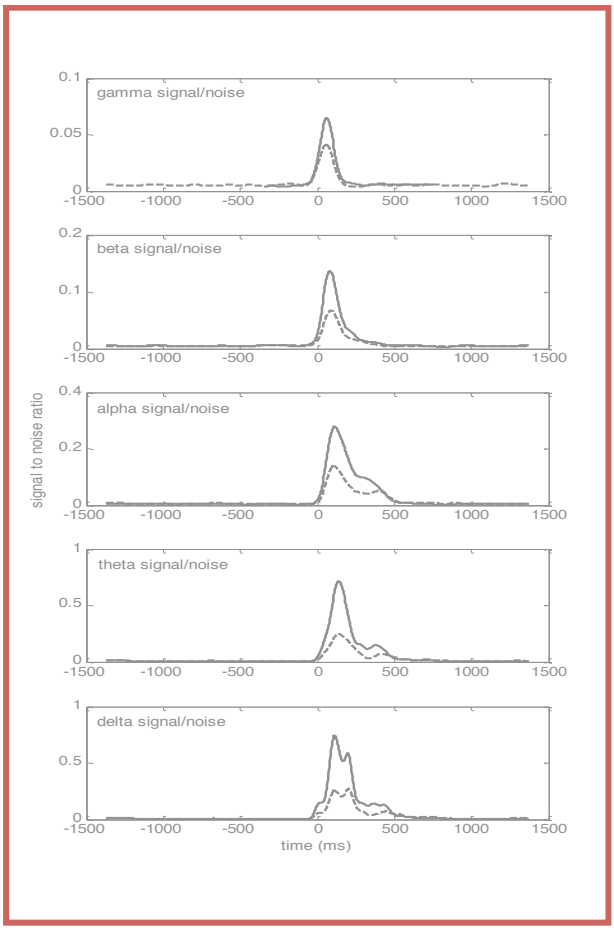

Figure 4. The ratio of evoked to induced power (signal/noise ratio) is decreased in schizophrenia across the entire frequency spectrum (Solid lines = Controls, Dashed lines = Patients)). Adapted from [1]

These results were in concordant with Winterer's findings of aberrant background neural noise and impaired recruitment in schizophrenia [46, 47]. The candidate further reflected in Work S1 that oscillatory analysis of the EEG had opened a new dimension in psychiatric research, which particularly lent itself to the framing of schizophrenia as an illness with neural disorder and noise at core concepts.

1.2.2. Exploring pre-stimulus/background EEG activity (Supplementary Work S2)

"Pre-stimulus theta power predicts the suppression of beta synchronization during motor response: Does a disrupted effect in schizophrenia reflect pathological baseline theta activity?" [14] [Please see Appendix 2]

In Work S2, the candidate further proposed that the pre-stimulus activity and interplay with post stimulus responses might be of considerable interest in schizophrenia. The functional role of pre-stimulus activity had received limited attention at the time of Work S2 [59]. Pre-clinically, enhanced alpha and theta interactions had been demonstrated during expectant states in cats and greater pre-stimulus alpha phase synchrony has been associated with reduced reaction times in an oddball task [60]. Pre-stimulus activity was thought to be task

specific in its regulation of executive control and a deficit in this effect has been implicated in schizophrenia [61]. Studies of the resting state in schizophrenia had shown an increased delta and theta activity [62].

Although many schizophrenia studies focused on the gamma (and beta) bands (associated with cognition [63, 64]) the candidate focused on fronto-central *theta* oscillations due to their link with dopaminergic function - implicated in the optimization of signal to noise ratio of local cortical microcircuits [52, 65, 66] and the prevailing neurotransmitter deficit model of the disorder. The ratio of D1/D2 dopaminergic signaling appears to modulate the excitability of prefrontal GABA- and glutamatergic neurons. Hence the reduction in D1/D2 receptor ratio reported in schizophrenia could provide a mechanism for destabilization of local cortical networks and increased neural 'noise' [52] [67]. Fronto-central theta is associated with both stimulus anticipation [68] and tasks involving working memory [69, 70].

Accordingly, in Work S2, the candidate tested the relationship between pre-stimulus theta activity and a putative oscillatory marker of executive function: beta event-related desynchronization (ERD) observable in event-related paradigms requiring a motor response (projecting from motor cortical and sub-cortical sources) and peaking at average response time [71] [72]. This beta ERD is thought to reflect a release of tonic inhibition of parieto-dependent motor networks for a learned action (i.e. sensory-motor transformation), and is followed by a rebound of beta power (event-related synchronization or ERS). The results of Work 2 showed preliminary evidence for a pre-stimulus theta/post-stimulus beta relationship detectable in health controls and significantly weakened in individuals with schizophrenia. This study was significant as one of the first studies to attempt to examine cross-spectral, pre/post stimulus relationships in schizophrenia.

1.2.3. Oscillatory measures prove more sensitive and relevant to task performance than conventional ERPs in ADHD (Work 1)

"Electrophysiological indices of abnormal error-processing in adolescents with attention deficit hyperactivity disorder (ADHD)" [15] [Please see page 46]

As discussed above, the candidate sought to identify EEG techniques that would yield more sensitive and clinically relevant measures in difficult to study clinical populations. One especially challenging population to study is children with Attention deficit hyperactivity disorder (ADHD). ADHD may have significant genetic, phenotypic and pathophysiological overlap with some features of schizophrenia [73]. Both disorders also involve abnormalities in dopamine neurotransmission, a system hypothesized to be involved in the mal-coordination of cortical activity discussed in section 1.2.2 and perhaps reflected in theta oscillations. ADHD

affords the further distinct advantage of allowing researchers to more readily manipulate dopaminergic tone (than in schizophrenia) via stimulant medications with more rapid onset and offset of therapeutic effects.

In the first study of its kind, the candidate applied (then novel) ITC analysis within a better-established visual go/no-go ERP paradigm (error-related negativity - ERN and Error positivity - Pe) with the hypothesis that it would more sensitively differentiate patients with ADHD from controls, and correlate more readily with clinical measures of executive function. Evoked theta power and ITC were measured in two time windows corresponding to those used for detection of the ERN and Pe. Whereas only a statistical trend was detected for a reduced Pe in the ADHD group, significant reductions were detected in evoked theta in the ERN window and theta ITC in both windows. Furthermore, theta ITC most strongly predicted post error slowing (a behavioral measure of response adjustment in trials immediately following an error) [15]. These findings were used to recommend the wider use of this novel EEG methodology in this clinical population.

The second significant contribution the candidate's work from this lab (University of Nottingham, UK) made to psychiatric EEG methodology was the adaptation and application of a novel artifact handling technique (independent component analysis [55]). Among the first clinical EEG studies to implement this technique, it allows researchers to *correct* rather than *reject* trials that contain artifact (an especially problem when studying children with ADHD who exhibit significant amounts of movement). This allows preservation of trials where conventional pre-processing techniques would warrant discarding of significant portions of hard-earned data, weakening a study's ability to detect a signal of interest.

1.2.4. From 'complex analyses' to analysing complexity (Supplementary Work S3)

"*Cannabinoids Generate Neural Noise in Humans: A Nonlinear Analysis of EEG Signals*" [16] [Please see Appendix 3]

Although oscillatory analysis revealed an additional dimension of the EEG (beyond ERP analysis) and allowed 'more complex' analyses (in a colloquial sense) to take place (e.g. pre-post stimulus interacts, isolating phase and amplitude, cross-spectral analyses), the actual mathematical complexity of the EEG signal was not being directly captured.

The term 'noise' in signal processing implies disorder or randomness. However, established measures of EEG 'noise' (induced and spontaneous baseline activity) are far from random in nature and reflecting a relationship (or rather lack of) with functionally-important, top-down processes such as attention and cortical tuning [74]. Therefore, our definition of 'noise' must

evolve beyond the activity's relationship to an event or task to fully capture disorder and complexity.

Lempel-Ziv Complexity (LZC) is a non-linear measure first developed to characterize the randomness of finite length sequences [75] and has been increasingly theoretically *and* empirically validated in the study of electrophysiological signals [76]. Its value reflects the number of different patterns or *words* contained in a sequence and the rate at which new words occur [75]. For random sequences (e.g. white noise) LZC approaches 1, while for regular/periodic sequences (e.g. seizure activity) it approaches 0 [77, 78]. Although not all sources of variation of LCZ are understood, in any given physiological signal, there likely exists a functionally optimal, intermediate level, with potential dysfunction at the extreme values.

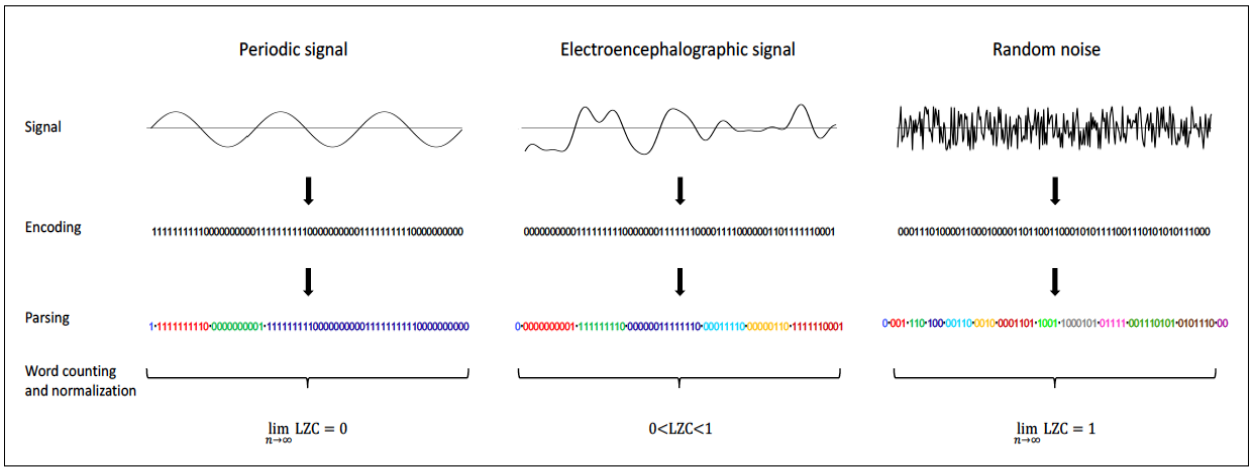

Figure 5. Lempel-Ziv complexity in periodic, electroencephalographic, and random signals. This figure depicts the steps followed to calculate LZC in three different types of signals: periodic (regular), electroencephalographic, and white noise. From top to bottom, the first step consists of coding the signal into a binary (1's and 0's) symbolic sequence; then the sequence is parsed in order to obtain the distinct symbolic subsequences or *'words'* forming it (for each type of signal, different words are shown as different color sequences separated by dots); finally, the number of distinct words is determined and the result normalized to obtain an LZC value that approaches 0 for a regular sequence and 1 for a random sequence (when the length of the signal (n) tends to infinity). Note that the number of distinct words is minimal for the periodic signal and maximal for random noise, while the number of words of the electroencephalographic signal lies between both extremes. Adapted from [79]

LZC's conceptual advantage as a biomarker of neural noise is that it more data-driven, reflecting a dynamic state of the system and not requiring the presence of a task for its definition. LCZ's practical advantages are that it is sensitive to both the power spectrum and temporal amplitude distributions, but is independent of absolute signal amplitude [79]. LCZ

represents a paradigm shift, but may be complementary to the aforementioned measures of cortical 'noise': signal to noise ratio (which is highly sensitive to inter-trial variations in timing) and baseline power (which is a gross measure dependent on the overall amplitude, rather than content, of the signal). LCZ has been measured in schizophrenia with mixed results, possibly attributable to burgeoning evidence that negative symptoms decrease, whereas positive symptoms increase, complexity [80-82].

Supplementary Work S3 was significant as the first ever report of increased neural 'noise' in a psychosis state induced by THC during a human laboratory study. Now, finally armed with a direct measure of EEG complexity, the candidate aimed to explore the prediction that increased EEG complexity, as a unifying principle in psychosis, would correlate highly with psychotomimetic effects. Work 3 of Part 2 represents this more extensive experiment, examining the potential utility of LCZ as a marker of psychosis states.

PART 2) THE PERSON: Advancing Clinical Research Approaches to Explore Psychosis

2.1 Overview of published work

- **WORK 2.** *Psychotomimetic and Cognitive Effects of Delta^9-Tetrahydrocannabinol in Laboratory Settings* [83]
  - **Contribution**: created outline and main points of the chapter, took overall responsibility for the material and wrote majority of text

- **WORK 3**. *The psychosis-like effects of Δ 9-tetrahydrocannabinol are associated with increased cortical noise in healthy humans* [79]
  - **Contribution:** significant contribution to the hypothesis, design and conduct of the EEG analysis and interpretation of the results, contributed to preparation of the manuscript

- **SUPPLEMENTARY WORK S4.** *Ketamine and depression* [84]
  - **Contribution:** Solely responsible for preparation of the work

- **WORK 4.** *Testing differences in the activity of event-related potential sources: important implications for clinical researchers* [85]
  - **Contribution:** equal primary contribution to design, conduct and reporting of the study

2.2 Commentary

The candidate had the opportunity to translate the basic science concepts and EEG methodology developed at the University of Nottingham, to more clinically oriented research within the Schizophrenia and Neuropsychopharmacology Group at Yale University, CT, USA.

Much of the candidate's prior study of psychosis had been in the context of recruited patients diagnosed with schizophrenia via conventional diagnostic criteria. However the value of such diagnostic classifications of psychotic disorders (based purely on clinical interview) had begun to be broadly challenged [9]. Schizophrenia is still being reimagined as group of disorders with multiple candidate genes, risk factors and underlying abnormalities and hence is both a heterogeneous and patho-physiologically complex syndrome [10, 12] [86].

In keeping with the idea of a complex system, outlined in the preface, this patho-etiological complexity would denote a high number of interacting, context-dependent, adaptive processes contributing to a similarly complex clinical syndrome. Therefore when recruiting

subjects to study psychosis on the basis of clinical interview and diagnostic classification, one can yield a patho-physiologically diverse group, potentially reducing the power to test the hypothesis in question. In response to this assertion, the NIMH launched the Research Domain Criteria (RDoC) initiative - but not without debate [87, 88]. It called for shifting the primary focus of research from diagnostic classifications to variations in neural circuitry - with levels of analysis progressing either 'upwards' to clinically relevant variables, or 'downwards' to the genetic and molecular/cellular factors [87]. One interpretation of RDoC is that subjects might for example be recruited on the basis of experiencing positive symptoms (such as specifically auditory hallucinations) and not by a diagnosis of schizophrenia. A key criticism of this approach was that it attempts to arbitrarily further split the construct of psychosis into a number of interacting domains of dysfunction [88] [89]. This critique is perhaps most challenging as it might encourage the treatment of psychosis as *complicated* rather than *complex* problem.

2.2.1 Addressing the patho-etiological complexity of psychosis with psychotomimetic drug models (Work 2)

"Psychotomimetic and Cognitive Effects of Delta^{9}-Tetrahydrocannabinol in Laboratory Settings" [83] [please see page 59]

An alternative to tackling the patho-etiological complexity faced when studying clinical psychosis is the study of experimentally induced psychosis (psychotomimetic drug models) in otherwise healthy individuals. This type of study recruits healthy controls (free of psychosis) and under laboratory conditions induces a transient psychosis state using a standardized administration of a medication or drug known to have predictable psychosis-like effects. These so-named psychotomimetic effects can include perceptual abnormalities (illusions and hallucinations), delusional beliefs and feelings, disorganization of thoughts and speech, and altered perceptions of self (such as dissociation). Some psychotomimetic drug models may also produce effects that resemble negative symptoms (i.e. apathy, anhedonia, alogia, asociality and avolition) and also impair several aspects of cognition (memory, attention and executive function). A more homogeneous psychosis *state* can be obtained, without complicating effects of *trait* features associated with heterogeneous clinical psychotic disorders. In other words, psychotomimetic drugs can simulate core elements of psychosis in the absence of some of the collateral deficits observable in complete clinical syndromes such as schizophrenia. Examples of such psychotomimetic agents include phencyclidine, ketamine, tetrahydrocannabinol (THC), amphetamine and lysergic acid diethylamide (LSD) [90] [84] [83].

Human laboratory Studies using THC, conducted since the 1970's, have reliably demonstrated a range of dose-dependent psychotomimetic and cognitive effects in healthy humans (as well as in individuals with cannabis use disorder, increased risk of psychosis, and schizophrenia). In Work 2 the candidate assimilates this literature and produces guidelines to clinical researchers seeking to conduct or draw inferences from this type of study. Broadly, deficits are observable in domains most relevant to schizophrenia: positive, negative, dissociative, and disorganization cluster symptoms and impairment in working and verbal memory [91] (see Table 3).

Subject Quote	Symptom
I thought you could read my mind, that's why I didn't answer	Suspiciousness/paranoia
I thought you all were trying to trick me by changing the rules of the tests to make me fail	
I could hear someone on typing on the computer… and I thoughts you all were trying to program me	
I thought you all were giving me THC through the BP machines and the sheets	
I couldn't keep track of my thoughts… they'd suddenly disappear	Formal thought disorder
It seemed as if all the questions were coming to me at once… everything was happening in staccato	
My thoughts were fragmented… the past, present and future all seemed to be happening at once	
I felt I could see into the future… I thoughts I was God	Grandiosity
The AC that I couldn't hear before suddenly became deafening	Perceptual abnormalities
I thought I could hear the dripping of the iv and it was louder than your voice	

Table 3. The quality of psychotomimetic effects reported by health individuals following the intravenous infusion of 2.5 or 5mg of THC, interpreted within common phenomenological domains of schizophrenia (adapted from [83], originally reprinted with permission from [91])

The acute administration of cannabinoids in tightly controlled laboratory settings allows for both a clearer inference of causality of effects and a more detailed characterization of those effects. In this way, they attempt to simplify a complex problem as a first step to understanding it. However they are not without limitations. The degree to which psychotomimesis reflects any other type of psychosis state remains subject to debate. Tight inclusion and exclusion criteria, operationalized cannabinoid administration and the inevitable influence of the laboratory setting on subjective effects experienced by the participant

constrain the generalizability and/or limit the interpretation of this type of study. Subjects may self-select due to past positive or negative associations with cannabis and/or laboratory-based research in general. Most notably, those who have experienced past adverse effects from cannabinoids are unlikely to volunteer for such studies. Despite providing a useful laboratory model of psychosis in humans, HLS using cannabinoids are unlikely to ever adequately replicate the *full* range of deficits observed in psychotic disorders and therefore can only provide a restricted, though penetrating, view [83].

2.2.2. Lempel-Ziv complexity promises a sensitive measure closely associated with psychosis symptoms (Work 3)

"*The psychosis-like effects of Δ 9-tetrahydrocannabinol are associated with increased cortical noise in healthy humans*" [79] [please see page 114]

Lempel-Ziv complexity was introduced above, as a nonlinear measure of signal randomness [16]. Work 3 reports the acute, dose-related effects of Δ9-THC on Lempel-Ziv complexity and signal power in 24 individuals who completed 3 test days during which they received intravenous Δ9-THC (placebo, 0.015 and 0.03 mg/kg) in a double-blind, randomized, crossover, and counterbalanced design. The larger study producing Work 3 was also significant as a multi-modal study of a single clinical phenomenon in keeping with the translational perspective of this thesis. For the larger study, outcomes were collected in the following modalities: subjective and objective behavior, cognition, vital signs, EEG, genetic screening of common psychosis relevant polymorphisms and serum cannabinoids. As hypothesized in Work 3, Δ9-THC increased neural noise in a dose-related manner. The candidate, drawing on the work presented in Part 1 and the ideas outlined in the preface, further hypothesized that Lempel-Ziv complexity (as more proximate measure complexity) would correlate highly with the THC-induced psychosis-relevant clinical effects, specifically positive and disorganization symptoms. The analysis in Work 3 confirmed a strong positive relationship, which was independent of total signal power. These results are consistent with a report that (a different measure of) EEG complexity is increased in the context of clinical decompensation in schizophrenia and normalizes with antipsychotic treatment [92].

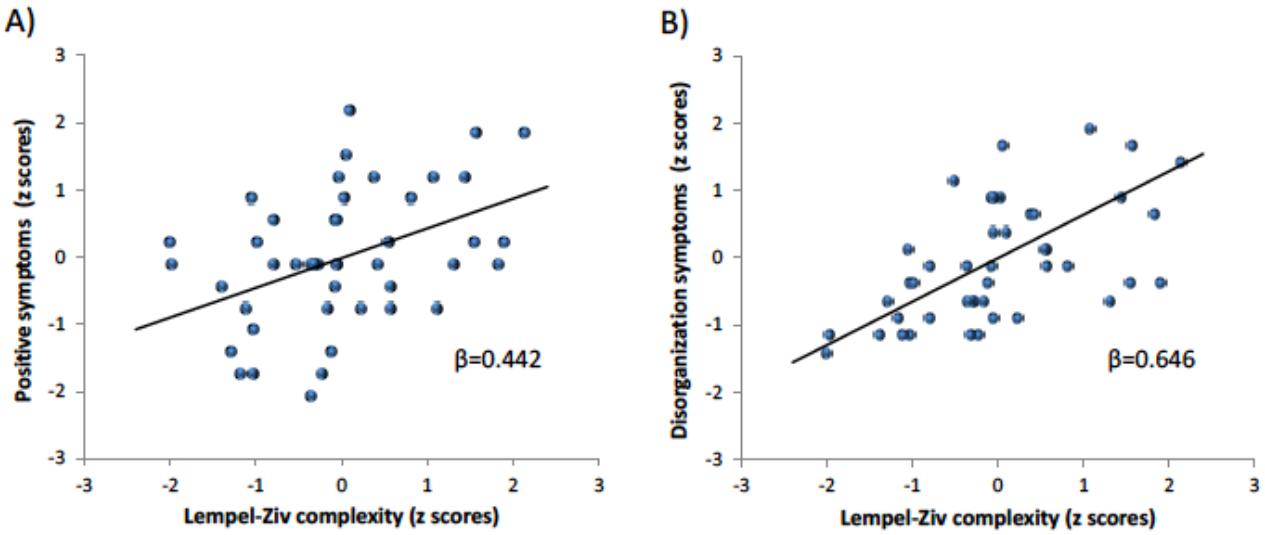

Figure 6. Δ9-THC-induced positive and disorganization symptoms versus Lempel-Ziv complexity uncorrected for signal power. The figure shows the linear regression lines and standardized coefficients of the positive (**A**) and disorganization (**B**) symptoms factors of the PANSS on Lempel-Ziv complexity (LZC) uncorrected for signal power. PANSS scores and LZC values are presented in z scores. Adapted from [79]

Of significant note, the level of correlation between LZC and these clinical effects exceed that of the major established psychosis biomarkers at time of publication [93]. The relative effect sizes are illustrated in the following figure. These results further lend support to a couple of assertions of this thesis – that the evolution of EEG methodology has yielded measures closer to the core pathophysiology of psychosis and secondly, that experimentally-induced psychosis states may hold inferential advantages over the study clinical psychosis (which can have significant confounding factors as a result of the underlying illness or its treatment).

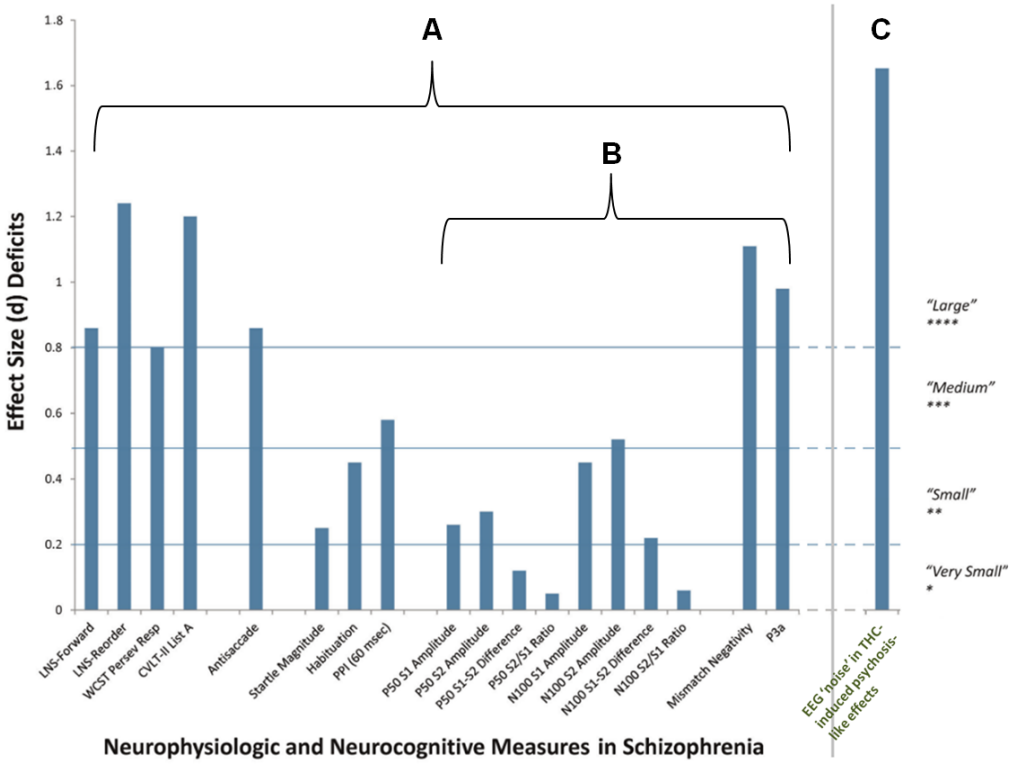

Figure 7. Contextualization of magnitude of Cohen's d effects size amongst established neurophysiologic and neurocognitive biomarkers in schizophrenia. A and B are adapted from [93] and C is based on the *r* value for the relationship between level of EEG noise and PANSS positive score from [79]. LNS=letter number span; WCST=Wisconsin Card Sorting Test; CVLT=California Verbal Learning Test; PPI=pre-pulse inhibition.

2.2.3. Embracing serendipity with caution: ketamine psychotomimesis and rapid antidepressant effects (Supplementary Work S4)

"Ketamine and depression" [84] [please see Appendix 4]

The psychoactive effects of THC in human laboratory studies (HLS) resolve spontaneously within a number of hours and have no reported long lasting effects [94]. This is also generally true of ketamine, another psychotomimetic drug with which the candidate has worked [95]. Ketamine's principal action in the brain is on *N*-methyl-D-aspartate (NMDA) receptors, where it blocks the action of the brain's principal excitatory neurotransmitter, glutamate. As a derivative of phencyclidine (PCP), ketamine shares some notoriety as a commonly abused club drug, going under the street names *K* and *Special K*. It is a schedule III controlled substance in the United States. At lower, so-called sub-anesthetic doses (at which

consciousness is largely preserved), ketamine produces dissociative (out-of-body) and hallucinogenic effects. These effects led to its early study in psychiatric research, as a pharmacological model of psychosis [84].

When conducting HLS with ketamine however, investigators serendipitously observed a longer lasting, rapid onset antidepressant effect in depressed subjects. This led to a line of experimentation that now shows promise for an entirely novel class of antidepressant and highlighted the complexity inherent in the patho-physiology of depression, but also ketamine's mechanism of action. In Supplementary Work S4, as ketamine's potential use as a rapid antidepressant begins to garner wider public attention, the candidate assimilates the history and evidence in order to examine ketamine's future value as psychiatric medication. Critically, Supplementary Work S4 argues for rigor in the face of this observed complexity (and hence uncertainty) – and weighing the risks and benefits of ketamine burgeoning use, which still continues largely on the basis of case report level evidence (and not large randomized, placebo-controlled trials) [84].

2.2.4 Applying novel methodologies to clinical research with rigor: catching a widespread error in interpretation of EEG source analysis in clinical studies (Work 4)

"*Testing differences in the activity of event-related potential sources: important implications for clinical researchers*" [85] [please see page 124]

A further example of the candidate's advocacy for the retention of methodological rigor when being challenged by the complexity of the brain is Work 4. As described above, spectral measures such as ITC broadened our view and understanding of the activity underlying ERPs in the temporal domain. *Spatially* however, new techniques were also emerging in the methods literature. The EEG only allows researchers to *infer* the underlying neural activity from the electrical potentials measured at each electrode site on the scalp. This is referred to as the inverse problem [96]. Source analysis techniques have been developed to estimate the location and activity of the underlying 'neural generators' of the scalp EEG.

Although there is theoretically no unique solution to the 'inverse problem', Low Resolution Electromagnetic Tomography (LORETA) was, and remains, a more commonly used technique [97]. LORETA's popularity may have been aided by its ease of use (incorporated into a user-friendly GUI interface) and it has been used on hundreds of scientific publications [98]. Unfortunately, perfunctory application and extension of this novel technique to compare clinical with control groups (for which the methodology was not fully developed) resulted in some inferential errors in at least eight studies. Work 4 alerted clinical researchers to this fact

and provided guidance on interpreting the results of LORETA in clinical research. The subtext of Work 4 is that perhaps at times, our hasty desire as researchers to explain (and simplify) observations of the brain's complexity may be premature or even misguided.

PART 3) THE ENVIRONMENT: Translating Principles of Complexity to Clinical Practice, Services Development and Education

3.1 Overview of published work

- **WORK 5.** *The Endocannabinoid System and Schizophrenia: Links to the Underlying Pathophysiology and to Novel Treatment Approaches.* [99]
    - **Contribution:** equal principal contribution to the concept, message and content of the paper

- **WORK 6.** *A Prescription for "Deprescribing" in Psychiatry* [100]
    - **Contribution:** equally responsible for the ideas and concepts in the paper

- **WORK 7.** *Psychopharmacology Prescribing Workshops: A Novel Method for Teaching Psychiatry Residents How to Talk to Patients About Medications.* [101]
    - **Contribution:** principal role in designing and disseminating this course and significant contribution to the text

- **WORK 8.** *Building Early Intervention Services for Psychotic Disorders: A Primer for Early Adopters in the US* [102]
    - **Contribution:** helped developed model for building such a clinical service (as medical director of STEP clinic) and made significant contribution to the text

3.2 Commentary

Part 3 outlines an array of related efforts to translate the key ideas and inferences from the methodological, basic science and clinical research of Parts 1 and 2 into clinical practice via the development of new treatments, optimization of health services and dissemination of related perspectives and skills through novel pedagogy.

Psychotic disorders, as complex problems within a complex system, warrant complex solutions. Sturmberg and Martin, 2013, suggest that one must work on multiple parts of the system and seek to *influence* it and not provide a unique solution [2]. Similarly, as discussed above, Glouberman and Zimmerman imply that one should neither be seeking a 'simple recipe', nor a 'complicated set of procedures', but rather a nuanced, optimistic, problem-solving stance, tolerant of uncertainty and the dynamics of system – which they compare to raising a child well [3]. Petticrew, 2011 offers urban regeneration programs as an example of a complex public health intervention. These programs target health outcomes and reduce health inequalities via the socio-economic determinants of health via complex packages of

interacting 'components': such as employment, education, income, crime and housing interventions. Petticrew also notes that services research conducted from a complex orientation could assess; how and whether these components work individually and together, interactions between multiple health and non-health outcomes, as well as the process by which these components bring about change [103].

3.2.1 Identifying more complex pharmaco-therapeutic targets relevant to psychosis (Work 5)

"The Endocannabinoid System and Schizophrenia: Links to the Underlying Pathophysiology and to Novel Treatment Approaches" [99] [please see page 129]

Despite the wide availability of conventional antipsychotics (sharing a common mechanism of blocking dopamine receptors) for over 50 years, psychotic disorders remain one of the most severe and difficult-to-treat psychiatric illnesses. While a range of alternative therapeutic targets, such as the glutamatergic system, have attracted attention (for negative symptoms and cognitive dysfunction [104]), novel treatments for the core positive symptoms of schizophrenia remain lacking [105].

The endocannabinoid system (ECS), despite being relevant to both the pathophysiology and treatment of psychotic disorders has been largely overlooked, and is differentiable from the dopamine neurotransmitter system as a brain homeostatic and neuromodulatory system. Cannabinoid-1 receptors are highly expressed in the brain regions implicated in the putative neural circuitry of schizophrenia, including the cerebral cortex, basal ganglia, hippocampus, anterior cingulate cortex, and cerebellum [106] where they interact with other key neurotransmitter systems implicated in psychosis: modulating presynaptic glutamate and GABA release [107] [108], enhancing dopaminergic function in the prefrontal cortex and hippocampus and inhibitory feedback on mesolimbic dopamine neurotransmission [109, 110]. Furthermore, given that psychotic episodes are commonly precipitated by stress and that schizophrenia has been hypothetically linked to disorders of lipid membranes, oxidative stress and more recently inflammation, it is noteworthy that endocannabinoids (e.g. anandamide) are increased in response to stress, possess intrinsic antioxidant properties, and are precursors of membrane lipids, leukotrienes, and prostaglandins. The endocannabinoid system is therefore ubiquitous, pleotropic and unique in its significant interplay with other major physiological systems [99, 111]. Framing it is as a complex system, contextualizes the uncertainty and contradictory results observed in the clinical literature examining the link between endocannabinoids and psychosis [83, 99].

In keeping with the above principles of influencing change in complex systems the candidate contributes in Work 5 the argument that in designing novel treatments that target the

endocannabinoid system, consideration of the context and stage of illness is crucial. The candidate further proposes that working with naturally occurring compounds with similarly complex mechanisms of action, such as cannabidiol (a secondary psychoactive constituent of marijuana with uncertain, wide ranging effects) and anandamide (the brain's principal endocannabinoid) may be a productive starting point.

3.2.2 Promoting principles of complexity in prescribing whilst minimizing harm: deprescribing (Work 6)

"A Prescription for "Deprescribing" in Psychiatry" [100] [please see page 134]

Despite uncertainties that continue to surround the mechanism of action of many psychotropics, in general, medications can be considered 'simple' interventions – they have predictable effects on a principal target (e.g. receptor). In contrast, the act of *prescribing* and *maintaining* a psychiatric medication regimen is a complex intervention – a multitude of interacting factors from biological (e.g. age and medication interactions), psychological (nocebo and placebo effect, psychodynamic meaning of the medication) and social (cost of medication, sources of environmental stress) may influence the ability for that prescription to mediate an impact on the target symptom or disorder.

As discussed above, a nuanced, optimistic, problem-solving stance, tolerant of uncertainty and the dynamics of system is essential when offering a complex intervention. The candidate hypothesized that emergent driving forces arising from the complexity of patient-prescriber relationships (perhaps echoing the inherent complexity of the patients psychiatric disorder itself) could adversely influence therapeutic alliance and prescribing outcomes with a range of negative effects (for example excessive dosing, inappropriate medication choice, non-adherence, irrational polypharmacy and nocebo effects). Many of these adverse effects may be symptomatic of a loss of nuance or *inappropriate simplifications* during the prescribing interaction (e.g. reduction to a linear or cursory transaction of symptom report and dose change).

For example, a patient suffering from an acute exacerbation of a psychotic disorder attends outpatient clinic with a very chaotic and complex presentation - disorganization of thought, hallucinations, paranoia, delusions, dysregulated behavior and stressors in their social environment (such as estrangement from their family and homelessness). The disorientation and discomfort often felt by the patient can be easy transmitted to the provider when faced with such an overwhelming admixture of issues, complicating efforts to make a clinical assessment and implement a treatment (inevitably a complex intervention). The antipsychotic dose was immediately doubled with remission of symptoms of positive symptoms over the

next week and the psychiatrist feels relieved and that dose continued for months (to prevent further relapse). Unfortunately, the patient's homelessness is not addressed, he feels disempowered, left out of the decision-making process surrounding the changes and he develops severe emotional flattening, cognitive dulling and bradykinesia attributable to side effects of increased antipsychotic dose (so called secondary negative symptoms) [112].

When viewed within the 'complex perspective', the exacerbation of psychosis is associated with increased neural, clinical and environmental complexity (or noise) for the patient. Most effective treatments may be framed as being able to organize or quiet this noise in some fashion (e.g. providing respite housing could simplify the client's social environment, or more judicious and collaborative dose titration). Unfortunately, in this vignette, the rapid and isolated dose increase perhaps represented a *reactive oversimplification* (an overzealous imposition of order) in the providers' hope (unconscious or otherwise) of imposing simplicity on a highly complex clinical scenario, and therefore proved misguided.

Due in part to limited durations of follow-up in efficacy trials of psychotropics, there remains a relative paucity of evidence for the effectiveness of open-ended continuation of many of these medications; moreover discontinuation studies have shown that there is a subset of patients that may not require continuous pharmacological treatment [113-115]. Despite this, even in the face of long-term side effects, psychotropic medications from all classes are continued unchanged for years, on the presumption of the initial risk/benefit calculation carried forward. Further, it has been observed that psychiatry is increasingly becoming a specialty in which polypharmacy has become the rule rather than an exception [116-118]. Prescriber discomfort, related to sitting with difficult patients, the prescriber's own anxieties as well as uncertainties around risk, prognosis and therapeutic adequacy, if unchecked, could theoretically lead to the irrational and counter-therapeutic prescription of medications. Furthermore, fear of precipitating a relapse might encourage 'inertia' surrounding potential medication regimen reduction or discontinuation.

Deprescribing has been previously defined (in the primary, palliative and geriatric medicine literatures) as the systematic process of identifying and discontinuing drugs in instances when existing or potential harms outweigh existing or potential benefits. It takes into account medical status, current level of functioning, patient values and preferences [119]. In doing so, the patient and prescriber recruits key providers (e.g. primary care provider, therapist and visiting nurse) and supports (e.g. peers, family and friends), in addition to expert consultants (e.g. pharmacist) to be involved in the process. Seeking to address irrational polypharmacy in additional to other potentially sub-optimal prescribing practices in psychiatry, Work 6 was significant as the first application of deprescribing to psychiatry and proposes some broad principles for clinical practice. The candidate's unique contribution includes attention to the

'complex perspective' in designing this approach. Specific principles integrated include: sitting well with uncertainty, paying attention to dynamic changes in risk/benefit ratios (and also the patient-prescriber relationship), seeking to *influence* a client's system of care holistically and comprehensively using multi-stakeholder/shared decision-making approach, remaining flexible and not insisting upon a unique solution.

Deprescribing psychotropic medications[a]

Step 1: Choose the right time

- Avoid times of crisis or acute phase of illness
- Ensure that the treatment alliance is well established
- Use caution when the patient is actively abusing substances

Step 2: Compile a list of all the patient's medications

- Document dose, route, expected duration, and original indication
- Document current therapeutic and adverse effects
- Estimate potential drug-drug interactions and future risk-benefit ratio

Step 3: Initiate the discussion with the patient

- What is the patient's knowledge and attitudes about the medications?
- What is the patient's perception regarding the benefits and risks of each?
- Explore the meaning of medication(s) to the patient

Step 4: Introduce deprescribing to the patient

- Inform the patient about potential indications for and the process of deprescribing
- Solicit ideas, concerns, and expectations
- Address any anxieties on the part of the prescriber, patient, family, or clinical care team
- Get family and caregiver buy-in

Step 5: Identify which medication would be most appropriate for a taper

- Collaboratively weigh pros and cons of deprescribing each medication
- Solicit the patient's preferences

Step 6: Develop a plan

- Set a start date and rate of taper
- Is a switch to another medication or formulation indicated?
- Reinforce alternative biopsychosocial strategies for addressing symptoms
- Inform the patient about expected and possible discontinuation effects and their timing
- Agree on a monitoring and follow-up schedule and crisis plan

Step 7: Monitor and adapt, if necessary

- Adjust rate of taper
- Treat discontinuation syndrome or relapse
- Abort or defer deprescribing

[a] Although the entire array of medications taken by a patient needs to be considered for deprescribing, psychiatrists may focus on psychotropic medications and provide the impetus for deprescribing of other medications through coordination with primary care physicians and pharmacists.

Figure 8. The 7 steps of deprescribing in psychiatry. Adapted from [100]

3.2.3 Teaching complexity in prescribing using complex pedagogy (Work 7)

"Psychopharmacology Prescribing Workshops: A Novel Method for Teaching Psychiatry Residents How to Talk to Patients About Medications" [101] [please see page 139]

Work 7 tests the principle that in order to teach a complex intervention (i.e. prescribing) a complex pedagogy is warranted. The candidate's contribution to Work 7 was as the principal designer of a novel course, classroom approach and curriculum for teaching physicians in advanced psychiatry specialty training (Yale Psychiatry Residency program). This course was developed at Yale University over 2 years before it was exported, implemented and tested at Columbia University, NY, USA.

Traditional psychopharmacology curricula tend to rely on lecture-based presentation of core knowledge. However, there are several limitations to this approach. First, there is a large body of literature demonstrating that lectures are a relatively ineffective means of transmitting content to adult learners [120]. Second, the act of good prescribing requires more than acquired knowledge: psychiatrists must draw upon the confluence of communication skills, ethics, therapeutic process and professional identity. Lastly, the ability to recognize and process anxiety that is evoked by the experience of prescribing is vital to a trainee's development [121, 122].

The key learning objective is that *residents will be safe and effective prescribers of psychotropic agents.* Instead of reviewing static material in a didactic format, classroom time was restructured so as to focus explicitly on behavioral proficiencies, influencing attitude and approach and allowing unique problem solving towards the central objective rather than enforcing a universal solution. To optimize active engagement with the material, each session incorporates self-directed learning ('flipped classroom'), skills, role-play, peer feedback, group process and modeling of using the 'complex perspective' in prescribing by the facilitator.

3.2.4 Implementing and disseminating the Coordinated Specialty Care model guided by the 'complex perspective' (Work 8)

"Building Early Intervention Services for Psychotic Disorders: A Primer for Early Adopters in the US [102] [please see page 146]

Recent changes in federal U.S. healthcare policy launched a national initiative towards specialty team-based models adapted to care for young individuals with recent onset psychosis. The RAISE (Recovery After an Initial Schizophrenia Episode) initiative, sponsored

by the NIMH (National Institute of Mental Health) [123] and the STEP clinic (Specialized Treatment Early in Psychosis) [124] helped define such Coordinated Specialty Care (CSC) services as a new benchmark for care across the U.S.. As the directorship of the STEP clinic, the authors of Work 8 were invited to offer guidance to early adopters and supplement resources with a focus on the process of setting up such programs. In doing so, this Work follows the principles of the complex perspective: not providing a unique solution to this task (such as a manualized approach) but seeking to engender and empower a flexible, optimistic problem-solving stance grounded by both guiding principles and a set of multi-stakeholder derived clinical benchmarks [125].

As medical director of the STEP clinic, the candidate's specific contribution to Work 8 surrounded multi-disciplinary and pluralistic clinical formulation and treatment planning, managing uncertainty in the medical workup, and psycho-socially informed medication management. Practically this translates into the clinical heuristics of: meeting a patient where they are, and working within their current frame of reference rather than attempting to impose order/enact a *reactive oversimplification* (e.g. countering a delusion or being inflexible around appointment times); striving for shared decision making around minimum effective dosing of antipsychotics (e.g. to avoid imposing medication compliance and precipitating side effects); simplifying medication regimens (e.g. monotherapy and increased use of long acting injectable antipsychotics), increased awareness and management of negative symptom syndromes and maintaining the patient in the minimally restrictive environment that safety allows (e.g. minimize hospitalization and advocate for 'jail diversion' when appropriate).

As introduced above, it is proposed that *reactive oversimplification* in the face of a *complex problem* like psychosis can do harm on any level of the disorder: exclusion and stigma from family and friends, disempowerment by paternalistic care, secondary negative symptoms from medications, long-term hospitalization or even incarceration. All stakeholders might benefit from remaining mindful of this potential dynamic and seek balance when interfacing with an individual suffering from a psychotic disorder.

Conclusions, significance and future directions:

This thesis has attempted to outline a perspective on translational research in psychiatry, informed by concepts of complexity. Acknowledging the brain as a complex adaptive system and psychiatric syndromes (such as psychosis) as complex problems, underlines the need to design both research methodologies that account for this complexity, as well as complex interventions to positively influence clinical course. Specifically, sub-optimal outcomes (inferential, in context of research and clinical, in the context of care) may arise when

reactive oversimplification occurs in the face of attempting to sit with high levels of complexity in the field of psychiatry. The continued advancement and rigorous application of novel multi-modal methodologies, closely informed by a holistic understanding of the syndromes under investigation, are vital to the future of psychiatric research. The presented work links converging lines of evidence to suggest that the broad construct of complexity (with its several connotations) may be germane to psychotic disorders (and other psychiatric disorders) on the level of the neuron, person and environment. More empirical evidence is necessary to test this assertion. However until this evidence exists, *complexity theory* could guide the generation of hypothesis-driven research, as well as clinical thinking in psychiatry. If the principles of *complexity science* (as with any new methodologies) are to be successfully applied to psychiatry, rigor will be necessary.

EEG measures of complexity may be more proximate to the core deficits in psychosis [15, 79]. Related biomarkers may be further developed towards predicting and monitoring clinical decompensation as well as treatment response [126]. Human laboratory studies of psychotomimetic drugs in healthy humans have their role, in simplifying the phenomenological and patho-etiological complexity, which can frustrate the study of psychotic disorders in clinical populations. Broader multi-modal and multi-level study designs (combining biophysical signals, individual phenomenology and even population level outcomes), alongside data mining techniques, may help to further characterize the complexity within psychosis (and perhaps even help re-classify the clinical syndrome itself).

Complex problems warrant complex interventions. These may include more nuanced approaches to drug development, prescribing, services design as well as clinical education of those providing these services. When attempting to care for individuals suffering from psychosis, all stakeholders would do well to remain mindful of the degree of complexity on multiple levels of the disorder and of any dynamics at play that might risk the unfavorable imposition of order.

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WORK 1

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Electrophysiological indices of abnormal error-processing in adolescents with attention deficit hyperactivity disorder (ADHD)

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Background: Impaired cognitive control has been frequently observed in children and young people with attention deficit hyperactivity disorder (ADHD) and might underlie the excessive hyperactivity and impulsivity in this population. We investigated behavioural and electrophysiological indices relevant to one domain of cognitive control; namely error processing. **Methods:** Adolescents aged 14 to 17 with ADHD (n = 23) and a typically developing control group (HC; n = 19) performed a visual go/no-go task. Electro-encephalography (EEG) data were collected simultaneously and response-locked error trials were averaged to derive two event-related potentials, the error-related negativity (ERN) and error positivity (Pe). Evoked theta power and inter-trial phase coherence (ITC) were measured in two time windows ('early' and 'late') equivalent to those used for detection of the ERN and Pe. **Results:** Analysis revealed normal ERN amplitude and a statistical trend for smaller Pe amplitude at a fronto-central electrode site in the ADHD group. The group also showed significant reductions in late evoked theta power and early and late theta ITC. Relationships between behavioural measures and ITC were different between groups, particularly for post-error slowing, a measure of strategic response adjustment on trials immediately following an error. **Conclusions:** The results reveal abnormalities in behavioural and electrophysiological indices of error processing in adolescents with ADHD and suggest that ITC is more sensitive than traditional ERP measures to error-processing abnormalities. **Keywords:** ADHD, electrophysiology, ERN, cognitive control, adolescence.

Attention deficit hyperactivity disorder (ADHD) is characterised by developmentally inappropriate levels of hyperactivity, impulsivity and inattentiveness (APA, 1994). At the cognitive level, children with ADHD show significant impairment in paradigms such as the go/no-go task and stop signal task (SST) in which inhibition of a prepotent or planned motor response is required (Nigg, 2001; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). In addition to increased error rates, which are taken as evidence of failures in the inhibitory process, children with ADHD show greater variability in response times and are also less likely to slow their responses on trials that immediately follow an error (post-error slowing) (Schachar et al., 2004; Sergeant & van der Meere, 1988), indicating a more general impairment in cognitive control, particularly response regulation. Crucial to the successful performance of tasks that require cognitive control, such as the go/no-go and SST, is error monitoring. To perform well, participants must detect and evaluate errors as they arise in order to make the necessary adjustments to their response strategies both immediately and over the course of the task. It is therefore important to establish whether deficits in response inhibition and in the adaptive control of response strategies in ADHD are accompanied by abnormalities in error monitoring.

Electrophysiology is the ideal approach for measuring cognitive functions which are carried out covertly, such as error monitoring. Two electrophysiological markers of error processing, the error-related negativity (ERN) and the error positivity (Pe), are obtained by averaging response-locked segments of electroencephalography (EEG) data on error trials. The ERN is a fronto-central negative voltage deflection peaking within 100 milliseconds (ms) of an erroneous response in forced choice reaction time (RT) tasks and in tasks requiring inhibition of a prepotent or ongoing response, such as the go/no-go task and SST (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Gehring & Fencsik, 2001). The ERN is followed by the Pe, a centro-parietal positive deflection occurring between 200 and 500 ms after an error. The ERN is hypothesised to reflect the activation either of an error detection system which responds in the event of a mismatch between the intended and actual outcome of a response (Gehring, Goss, Coles, Meyer, & Donchin, 1993; Holroyd & Coles, 2002) or of a general conflict monitoring system which increases activity when competition between alternative response sets is high (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999); errors being one example of high response conflict. Whereas the ERN is thought to be triggered relatively

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automatically, the Pe has been suggested to index conscious response evaluation (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001; O'Connell et al., 2007) and to be related to response adjustment strategies such as post-error slowing (Hajcak, McDonald, & Simons, 2003). Functional dissociation of the ERN and Pe is supported by source-localisation studies seeding them to different regions of anterior cingulate cortex (ACC) (Mathalon, Whitfield, & Ford, 2003) and by developmental studies showing that the ERN increases non-linearly throughout childhood and adolescence whereas the Pe does not differ in amplitude between children and adults (Davies, Segalowitz, & Gavin, 2004; Ladouceur, Dahl, & Carter, 2004; Santesso, Segalowitz, & Schmidt, 2006; Wiersema, van der Meere, & Roeyers, 2007). Investigating behavioural and electrophysiological indices of error monitoring in ADHD will provide information as to which aspects of the error monitoring system are deficient in this population and how these abnormalities relate to deficits in cognitive control at the behavioural level.

Research investigating the ERN and Pe in children with ADHD has produced mixed results. Reduced ERN amplitude was reported by one study using the SST (Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005) and two others using the Eriksen Flanker task (Albrecht et al., 2008; van Meel, Heslenfeld, Oosterlaan, & Sergeant, 2007). However, two studies using the go/no-go task have found normal ERN amplitude, reduced Pe amplitude and reduced post-error slowing in children (Wiersema, van der Meere, & Roeyers, 2005) and adults (Wiersema, van der Meere, & Roeyers, 2009) with ADHD, indicating intact automatic error detection (normal ERN amplitude) with faulty error evaluation (reduced Pe amplitude) resulting in a failure to adjust response strategies following an error (lack of post-error slowing). One study using the Eriksen Flanker task reported normal ERN and reduced Pe amplitude in children with ADHD but normal post-error slowing (Jonkman, van Melis, Kemner, & Markus, 2007), whereas another Flanker study found the opposite profile (reduced ERN, normal Pe) (Albrecht et al., 2008). A novel finding of enhanced ERN amplitude in ADHD children compared with typically developing controls has been reported (Burgio-Murphy et al., 2007) and might be attributable to the use of a simple task aimed at equating performance between groups. Research to date therefore suggests that abnormalities at either stage of error processing are not reliably present in ADHD and may depend on task design. The finding of normal ERN with reduced Pe in adults with ADHD (Wiersema et al., 2009) suggests that this profile may be a stable trait marker, present throughout the ADHD lifespan. However, considering the mixed results in this field, further work is needed to replicate this finding and also to determine whether this profile occurs in adolescents with ADHD.

ERPs provide useful information about the temporal aspects of cognitive processes but the averaged waveform may include several overlapping subcomponents, each with different phase and frequency characteristics (Yordanova, Falkenstein, Hohnsbein, & Kolev, 2004). In recent years, time-frequency analysis of EEG data has become more prevalent, revealing important information about frequency-specific oscillations which are time- and phase-locked to an event of interest and which are believed to be crucial to the coordination of activity in different brain regions (for a recent review of methods and approaches, see Roach & Mathalon, 2008). Recent research has shown that the ERN can be largely accounted for by an increase in evoked (event-related) theta power and inter-trial phase coherence (ITC) following an error (Luu, Tucker, & Makeig, 2004; Trujillo & Allen, 2007; Yordanova et al., 2004). In ADHD there is evidence of abnormal spontaneous (non-evoked) neuronal oscillations in the form of increased theta/beta ratio (reviewed in Barry, Clarke, & Johnstone, 2003) and one study has shown increased evoked theta power on target trials in an auditory oddball task in children with ADHD (Yordanova, Heinrich, Kolev, & Rothenberger, 2006). It is unknown whether young people with ADHD show abnormalities in error-related theta oscillations. Applying time-frequency analysis methods to the investigation of error monitoring in ADHD may help characterise the nature of abnormalities in this population.

First, this study sought to investigate whether the ERN/Pe abnormalities identified in children with ADHD are also present in adolescents with ADHD. Second, we included other electrophysiological measures, evoked theta power and ITC, to determine whether the ADHD group show abnormalities in the phase and amplitude of oscillations in the theta band. EEG data were collected from adolescents aged 14 to 17 with a diagnosis of ADHD and a control group of typically developing adolescents, while they performed a go/no-go task. We predicted significantly reduced ERN and Pe amplitudes and decreased post-error slowing in the ADHD group. We also predicted significantly less evoked theta power and ITC in the ADHD group.

Method

Full ethical approval for the study was granted by the Trent Multi-Centre Research Ethics Committee (MREC) and by the Research and Development department of Nottinghamshire Healthcare NHS Trust. Participants were 23 adolescents with ADHD (ADHD) (21 males, mean age = 16.20 ± .28 years) and 19 healthy control subjects (HC) (10 males, mean age = 16.14 ± 2.03 years). All were aged 14 to 17 years and were free from current significant substance abuse and neurological disorder, with IQ at least 70 on the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) (see Table 1 for

mean IQ). Participants were provided with written information and gave fully informed consent if aged 16 years or older; parental consent (with participant assent) was obtained for those aged less than 16 years. There were no significant differences between groups in age ($t(40) = .831$, $p > .1$) or parental socio-economic status, measured using the National Statistics for Socio-Economic Classification (Statistics, 2004) ($\chi^2 = 5.850$, $p > .1$). The ADHD group had a significantly higher male:female ratio than the HC group ($\chi^2 = 8.05$, $p < .01$).

The samples included in the present analysis were drawn from a larger study comparing mental health, cognitive function and brain activity in young people with schizophrenia; their siblings; healthy adolescents and adolescents with ADHD (see Groom et al., 2008). In this analysis, we focus on the HC and ADHD groups to enable a fuller exploration of error-processing abnormalities in adolescents with ADHD. Furthermore, because ERN amplitude has been shown to fluctuate during adolescence and because the full HC and ADHD groups in the main study differed significantly in mean age, for the present analysis we selected participants aged 14 to 17 years from the HC and ADHD groups. This age range was chosen because only two participants in the ADHD group were older than 17 (1 aged 19; 1 aged 20) and the sub-sample was therefore not very different, quantitatively or qualitatively, from the original sample. Sample characteristics are described below.

ADHD group

Forty-six young people aged 14 to 21 years with a clinical diagnosis of ADHD were referred to the study team by consultant psychiatrists and other healthcare professionals. Of those contacted, 34 were willing to take part and thorough psychiatric assessment was conducted using the Parental Account of Childhood Symptoms (PACS; Taylor, Schachar, & Hepstinall, 1993). This is a semi-structured interview conducted with parents/carers of children who are showing signs of ADHD. Parents are asked to rate the presence/severity of each of a range of behaviours indicative of the core symptoms of ADHD: hyperactivity, impulsivity, inattentiveness. The information obtained from the PACS interview, the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) (completed by parents and self-rated) and from the medical records of each potential participant was reviewed by 3 psychiatrists in a consensus diagnostic conference to determine whether criteria for a DSM-IV diagnosis of ADHD combined type (DSM-IV code: 314.01) were met and that each case was free from other major psychiatric disorders, except conduct disorder (CD) and oppositional defiant disorder (ODD). All satisfied these criteria. However, 3 with IQ less than 70 were excluded and 3 were excluded due to scoring greater than 22 on the Social Communication Questionnaire (Rutter, 2003), a threshold used to detect possible pervasive developmental disorder. Contact was lost with 1 participant and 2 did not complete ERP testing. For this analysis, 2 participants aged over 17 years were excluded, leaving a sample of 23. All participants were receiving stimulant medication which was withdrawn 24 hours before testing.

Healthy control group (HC)

Healthy control participants aged 14–21 years were recruited to the main study from local schools and further education centres and from the University of Nottingham, UK. Exclusion criteria were: score greater than 5 on the hyperactivity-inattentiveness subscale of the SDQ (parent- and self-rated); major psychiatric disorder and/or family history of psychosis (assessed using the Schedules for Clinical Assessment in Neuropsychiatry, Wing et al., 1990), reading/language disorder (assessed by self-report). Of an initial sample of 89 recruited to the main study, 12 were excluded (6 above SDQ cut-off; 1 family history of psychosis; 2 reading/language disorder; 3 dyslexia), contact was lost with 1 and 2 withdrew, leaving 74 potential participants. Time constraints made it impractical to test all participants; 36 individuals who provided a pairwise match to the siblings of schizophrenia patients recruited to the main study were selected. Of these 36 participants, 1 was unable to complete all ERP testing. For this analysis 16 participants aged over 17 years were excluded, leaving a final sample of 19.

Table 1 Group comparisons of clinical and behavioural measures

	HC	ADHD	Group difference
SDQ Hyp-Inattentive[a]	1.25 (.25–3.75)	9.00 (7.00–10.00)	$z = 5.25$**
SDQ Conduct problems[a]	1.00 (.00–2.00)	6.00 (3.00–9.00)	$z = 4.80$**
IQ[b]	105.16 (13.33)	93.41 (12.86)	$t = 2.87$**
Error rate[b]	.56 (.17)	.67 (.14)	$t = -2.116$*
d-prime[b]	1.40 (.6)	.69 (.45)	$t = 4.92$**
Criterion[b]	−.72 (.09)	−.75 (.07)	$t = 1.86$#
Hit RT[b]	327.58 (27.79)	336.76 (23.14)	$t = -1.33$
Error RT[b]	296.22 (21.92)	296.08 (16.61)	$t = .03$
Hit RT_SD[b]	73.91 (18.06)	93.39 (15.55)	$t = -3.67$**
Post-error slowing[b]	21.32 (30.28)	22.86 (37.78)	$t = -.17$

SDQ = Strengths & Difficulties Questionnaire; hyp-inattentive = hyperactivity-inattentiveness sub-scale of SDQ. # $p < .1$; * $p < .05$; ** $p < .01$.

[a]Data are median (inter-quartile range). Group differences were tested using Wilcoxon independent-samples non-parametric test.

[b] Data are mean (standard deviation). Group differences were tested using independent-samples parametric *t*-test.

Median scores on the SDQ hyperactivity-inattention and conduct problems sub-scales of the SDQ are shown in Table 1.

Go/no-go paradigm

The letters 'X' and 'K' were presented on a flat-screen LCD monitor. Stimulus duration was 250 ms and inter-stimulus interval was randomly jittered between 1.5 and 2.5 seconds. The stimuli were 400 by 400 mm equating to 3 by 3 degrees of visual angle. Participants were instructed to press the 'M' key as quickly as possible when the letter X (the frequent 'go' stimulus) appeared, but to withhold the response if a letter K (the infrequent 'no-go' stimulus) appeared. There were 304 trials in total, with 80% go trials. The task was split into 4 blocks of 2.5 minutes with a short rest period between blocks. To ensure that participants developed a strong prepotent response to the go stimulus, responses occurring later than 450 ms after stimulus onset were followed by the word 'TIME' appearing on-screen 900 ms after stimulus onset. This served as a reminder to participants to increase their response speed. This manipulation ensured that the task challenged inhibitory processes and produced sufficient numbers of error trials for analysis. Group mean error rates indicate that this was successful (see Table 1). The proportion of hits (correct responses to go stimuli) and errors (responses to no-go stimuli) were used to calculate d-prime (z (hit rate) – z (error rate)) and Criterion (–.5*z(hit rate) + z(error rate)). These indices provide information about the relationships between hit rate and error rate which cannot be obtained by considering each in isolation. D-prime is a measure of target sensitivity (e.g., high values reflect high hit rate and low error rate, indicating high sensitivity) and Criterion represents response threshold (e.g., high values reflect low hit and error rates, indicating a cautious response style). Distributional differences between hit rate and error rate are removed by transforming each into Gaussian distributions (*z*-scores). Post-error slowing was measured as the difference between mean RT for hit trials following an error and hit trials not following an error. Mean RT was measured on go trials with response occurring within a 100–900 ms time window ('Hit RT'). RT variability was measured as the inter-trial standard deviation of RT on Hits trials ('Hit RT_SD').

Electrophysiological recording

Voltage potentials were recorded at the scalp using 128 active silver/silver chloride (Ag/AgCl) electrodes (Active II system, Biosemi, Amsterdam) positioned according to the 10-5 system (Oostenveld & Praamstra, 2001). Eye movements were recorded from flat, sintered Ag/Ag-Cl electrodes placed adjacent to the outer canthus of each eye and vertically, at the inner-orbital ridge below each eye. Additional flat electrodes were placed on the right and left mastoids and the tip of the nose. The raw data were recorded using a referential montage with each electrode referenced to the Common Mode Sense (CMS) located immediately to the left of electrode Cz. Data were filtered at .1 to 100 Hz and digitised at 256 Hz.

Electrophysiological data processing

Analysis was carried out using Brain Vision Analyser, version 1.05 (Brain Products, Germany). Data were re-referenced to the nose electrode and filtered with Butterworth zero-phase filters at 1.0 and 20 Hz. Ocular artefacts were corrected using the Gratton regression method (Gratton, Coles, & Donchin, 1983); the left vertical ocular reference channel and right frontal scalp electrode were reference points. Further data processing was conducted on error trials only, which were defined as all no-go trials with a response occurring within a 0–700 ms time window. Data were corrected to a pre-stimulus baseline (−500 to −200 ms) before removal of epochs with amplitudes exceeding −90 and +90 μV and derivation of response-locked epochs 1500 ms in length with 500 ms preceding the response. One dataset with only 5 trials available for average was excluded from the ADHD group, leaving 22 datasets available for analysis. The remaining participants all had 18 trials or more per ERP average (HC group 32.42 ± 10.54; ADHD group 36.27 ± 8.37; $t(38) = -1.522$, $p > .1$).

ERP analysis. Based on inspection of group average ERPs (see Figure 1) the ERN was defined as the maximum negative peak within −50 to 100 ms of the response. The Pe was defined as the maximum positive peak within 100–350 ms of the response. The ERN was measured at Fz, FCz and Cz and the Pe at FCz, Cz and Pz on the basis of previous research (Falkenstein et al., 2000) and because inspection of the data confirmed this topography (see Figure 2). Peak amplitudes and latencies were exported for analysis.

Analysis of evoked theta power and ITC. Calculation of evoked power and ITC was conducted in MatLab using EEGlab (Delorme & Makeig, 2004). Epochs of −500 to 1000 ms centred on response were decomposed using 320 overlapping discrete-windowed Fourier transforms of 250 ms (zero-padded to 1000 ms) to give a frequency resolution of 1 Hz and sampling rate of 3.91 ms. Further analysis was restricted to the theta band (4–7 Hz). Evoked activity was computed as the absolute power (μV^2) of the averaged time-domain signal across trials. Inter-trial phase coherence (ITC), a measure of the degree to which the phase of the evoked response aligns across trials, independently of amplitude, was computed (Delorme & Makeig, 2004). A value of 0 represents no consistency in the phase of the evoked response across trials; 1 represents perfect phase consistency. Two time windows of −50 to 100 ms and 100 to 350 ms were chosen to correspond to the windows used to detect the ERN and Pe, respectively. Within these windows mean evoked power and ITC were calculated for each dataset. Evoked theta power measures were logarithm-transformed ($\log_{10}$) to correct non-normal distribution. The following indices were used in statistical analysis: early evoked theta power (log); late evoked theta power (log); early theta ITC; late theta ITC.

Statistical analysis

Behavioural data. Independent-samples *t*-tests were conducted to compare the HC and ADHD groups on

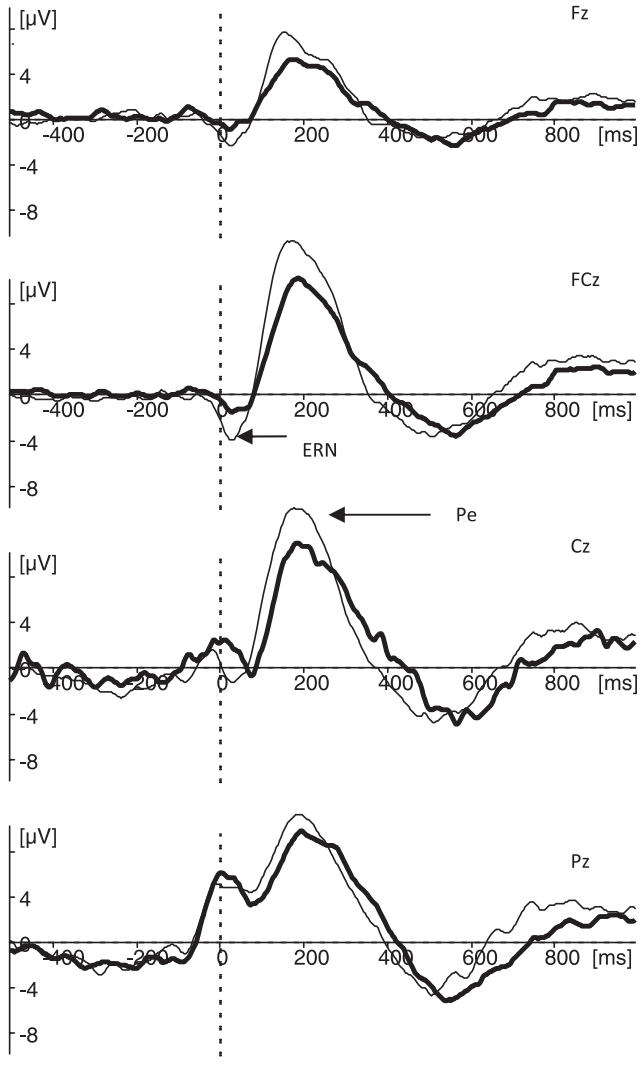

Figure 1 Group average waveforms at midline electrode sites. Each plot shows amplitude on the y-axis in microvolts (μV) and time in milliseconds (ms) on the x-axis at the following midline electrode sites: Fz (frontal); FCz (fronto-central); Cz (central); Pz (parietal). Vertical dashed line indicates response-onset; the HC group are shown by the thin line; the ADHD group by the thick line

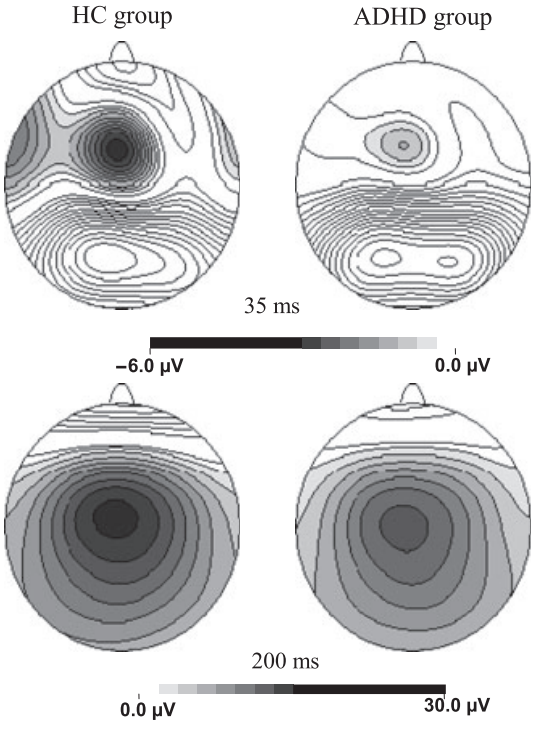

Figure 2 Group scalp maps of ERN and Pe amplitudes. The figure shows the topography of the ERN (top panel) and Pe (bottom panel) in HC and ADHD groups at the time points of maximal amplitude in the HC group (35 ms for the ERN; 200 ms for the Pe). The darkest shade represents maximum amplitude in both plots; negative amplitude for the ERN and positive amplitude for the Pe. White represents '0 μV' in both plots

d-prime, Criterion, Hit RT, Hit RT_SD, Error RT, and post-error slowing.

Electrophysiological data. Separate mixed-design ANCOVAs with age as covariate were conducted on each of the following measures: ERN latency; ERN amplitude; Pe latency; Pe amplitude; early and late evoked theta power; early and late theta ITC. Each ANCOVA included 1 between-groups factor with two levels (HC; ADHD) and 1 within-subjects factor, Electrode with 3 levels: Fz, FCz, Cz for analysis of the ERN, early evoked theta power and ITC; FCz, Cz, Pz for analysis of the Pe, late evoked theta power and ITC. Greenhouse–Geisser adjusted results are reported where necessary. Significant main effects of Electrode were followed with Helmert contrasts. Group*Electrode interactions significant at $p < .05$ and trends towards significance ($p = .05$ to .1) were explored further by investigating inter-electrode differences within groups using repeated measures ANOVA and by comparing the HC and ADHD groups at each electrode site with univariate ANCOVAs.

Covariates: Age was covaried in all analyses to correct for the lack of pairwise age-matching between groups and because there were significant correlations between age and several electrophysiological measures (Pe amplitude, late evoked theta, late ITC) in the HC group which were non-significant in the ADHD group. It was not possible to control gender effects because there were only 2 females in the ADHD group. However, there were no significant effects of gender in the HC group and removal of the 2 female ADHD participants did not change the results. To test the effects of IQ and CD/ODD symptoms on the results, all analyses were conducted with and without IQ and scores on the 'conduct problems' sub-scale of the SDQ included as additional covariates with age. Results remained robust to inclusion of IQ and other covariates and results are reported without covariates.

Relationships between electrophysiology and behaviour. Within-groups Pearson's correlation coefficients were calculated between each of the

behavioural variables (d-prime, Criterion, Hit RT, Hit RT_SD, Error RT, post-error slowing) and theta ITC in the early and late time windows at FCz, with age effects controlled. Calculations were restricted to these ITC variables to reduce the total number of correlations computed and were conducted with age controlled to prevent between-group differences in developmental factors masking group differences in relationships between behaviour and ITC. Group differences in correlation coefficients were examined by first applying the Fisher *z*-transform to normalise each correlation coefficient and calculating the *z*-score of the difference between the transformed correlations.

Results

Group comparisons of behavioural and electrophysiological measures

Group comparisons of behavioural data are shown in Table 1.

ERPs: Group averaged ERP waveforms are presented in Figure 1. Figure 2 presents scalp maps for each group showing midline topography for both components. ERP amplitudes and latencies, evoked power and ITC are shown in Table 2. There were no significant latency differences between groups; for brevity the analysis is not presented.

For ERN amplitude, there was no significant effect of Group ($F(1,37) = 1.779$, $p > .1$) or Group*Electrode interaction ($F(2,74) = 2.515$, $p > .1$). Analysis of Pe amplitude revealed a significant Group*Electrode interaction ($F(2,74) = 5.644$, $p = .006$). This was explored further by examining the main effect of electrode within each group and by exploring group differences at each electrode site. There was a significant effect of Electrode in the HC group only ($F(2,34) = 3.9$, $p = .03$) with greater amplitude at Cz than Pz ($p = .02$). Univariate ANCOVAs revealed a trend towards a significant group effect at FCz only ($F(1,37) = 2.919$, $p = .096$).

To determine whether the Group*Electrode interaction remained significant when overall amplitude differences between groups were controlled, repeated measures ANCOVA was conducted on vector normalised (McCarthy & Wood, 1985) Pe amplitudes. The interaction was significant ($F(2,74) = 3.190$, $p = .04$).

Evoked theta power: Analysis of evoked theta in the early time window revealed no significant main effects or interactions (all $p > .1$) but in the late time window there was a significant Group*Electrode interaction ($F(2,74) = 4.349$, $p = .018$). Further analysis revealed a significant effect of Electrode in the ADHD group only ($F(2,40) = 3.533$, $p = .04$) with greater amplitude at FCz than Cz and Pz combined ($p = .02$). Univariate ANCOVA revealed greater power in the HC group at FCz only ($F(1,37 = 5.018$, $p = .031$).

Table 2 Descriptive data for electrophysiological measures

	Latency		Amplitude	
	HC	ADHD	HC	ADHD
ERN[a]				
Fz	36.19 (31.21)	25.48 (49.81)	−1.77 (2.45)	−1.85 (1.63)
FCz	32.32 (31.47)	31.93 (42.20)	−2.68 (4.32)	−1.62 (2.48)
Cz	33.11 (36.17)	43.48 (42.88)	−.70 (4.42)	−.02 (3.78)
Pe[a]				
FCz	200.12 (48.01)	207.03 (52.43)	10.56 (4.14)	7.86 (3.68)
Cz	194.22 (37.92)	215.63 (58.65)	11.55 (4.29)	9.67 (3.90)
Pz	191.44 (66.63)	209.69 (73.13)	9.52 (3.09)	8.66 (4.06)
Early evoked theta[b]				
Fz	–	–	3.39 (.47)	3.28 (.41)
FCz	–	–	3.81 (.45)	3.52 (.38)
Cz	–	–	3.70 (.48)	3.60 (.32)
Late evoked theta[b]				
FCz	–	–	3.93 (.36)	3.67 (.33)
Cz	–	–	3.88 (.37)	3.73 (.41)
Pz	–	–	3.53 (.36)	3.49 (.35)
Early theta ITC[c]				
Fz	–	–	.33 (.14)	.28 (.09)
FCz	–	–	.38 (.13)	.28 (.11)
Cz	–	–	.37 (.14)	.29 (.11)
Late theta ITC[c]				
FCz	–	–	.45 (.18)	.33 (.10)
Cz	–	–	.45 (.18)	.36 (.13)
Pz	–	–	.34 (.15)	.29 (.10)

[a]Mean (SD) for ERN and Pe latency (ms) and amplitude (μV) at each relevant electrode site: Fz (frontal); FCz (fronto-central); Cz (central); Pz (parietal).
[b]Mean (SD) for the logarithm of evoked theta power (originally expressed as μV^2) at each electrode.
[c]Mean (SD) for inter-trial phase coherence (ITC) at each electrode.

Theta ITC: Group*Electrode interactions were found for early ($F(2,74) = 7.485$, $p = .002$) and late ($F(2,74) = 5.468$, $p = .012$) theta ITC. Further analysis revealed significant effects of Electrode in the HC group for early theta ITC ($F(2,34) = 5.181$, $p = .02$) with lower ITC at Fz than Cz and FCz combined ($p = .03$) and greater ITC at FCz than Cz ($p = .03$) and in the ADHD group for late theta ITC ($F(2,40) = 3.491$, $p = .04$) with greater ITC at FCz than Cz and Pz combined ($p = .003$). Univariate ANCOVAs comparing groups at each electrode showed significant effects at Fz in the early time window ($F(1,37) = 10.901$, $p = .002$) and at FCz in the late time window ($F(1,37) = 6.621$, $p = .014$).

Relationships between behavioural measures and ITC

Correlations between theta ITC at FCz and behavioural measures, corrected for age, are presented in Table 3.

Discussion

This study compared adolescents with ADHD and typically developing controls on behavioural and electrophysiological indices of error processing. The ADHD group had significantly lower d-prime than the control group but equivalent response speed and equivalent post-error slowing, suggesting a failure to adopt a more conservative response style despite poor performance. The ADHD group also showed greater RT variability on go trials, indicating moment-to-moment fluctuations in attention. Analysis of ERN and Pe amplitudes revealed no group differences or group*electrode interactions for the ERN but a group*electrode interaction for the Pe. Further analysis of the interaction revealed that Pe amplitude in the HC group differed significantly between electrodes (greatest amplitude at Cz) whereas inter-electrode differences in the ADHD group were not statistically significant. Additional analysis conducted on normalised amplitudes confirmed topographical differences between groups, although it should be noted that this approach has limitations (Urbach & Kutas, 2002). Simple main effects analysis on the original (non-normalised) data also identified a trend towards greater amplitude in the HC group than the ADHD group at FCz, indicating a weak reduction in Pe amplitude, but not ERN amplitude, in the ADHD group. This conflicts with previous reports of significantly reduced ERN in children with ADHD (Albrecht et al., 2008; Liotti et al., 2005; van Meel et al., 2007) but is consistent with findings of reduced Pe with normal ERN (Jonkman et al., 2007; Wiersema et al., 2005). The results provide tentative support for previous work showing a profile of normal ERN with smaller Pe in children (Wiersema et al., 2005) and adults (Wiersema et al., 2009) with ADHD, suggesting that the profile may be stable throughout development, although further replication is needed. Current hypotheses are that the Pe reflects subjective/emotional evaluation of error commission (Falkenstein et al., 2000; Nieuwenhuis et al., 2001; O'Connell et al., 2007) suggesting that the reduced Pe identified here and in previous studies of ADHD reflects a failure to process the emotional significance of errors, possibly because as errors increase in frequency, they become less salient (Falkenstein et al., 2000).

Evoked theta power and ITC

Analysis revealed group*electrode interactions for evoked theta power in the late time window and theta ITC in both the early and late time windows. Again, further exploration of these interactions indicated topographical differences between groups and also suggested that at fronto-central electrode sites, there were group differences in late evoked theta power and in early and late theta ITC with both indices being significantly reduced in the ADHD group. Previous research has shown that ERN amplitude can be largely explained by evoked power and phase coherence in the theta band (Luu et al., 2004; Trujillo & Allen, 2007). It therefore seems feasible to suggest that error processing, as indexed by the ERN and Pe, is, to some extent reflected by theta ITC in

Table 3 Correlations between theta ITC and behavioural measures

	Early theta ITC at FCz			Late theta ITC at FCz		
	HC[a]	ADHD[a]	z[b]	HC[a]	ADHD[a]	z[b]
D-prime	.50*	.24	.90	.47*	.19	.94
Criterion	.20	.21	−.l8	.09	.02	.21
Hit RT	.25	.24	.03	−.17	−.21	.12
Error RT	.01	−.18	.57	−.29	−.37	.26
Hit RT_SD	−.34	.11	−1.37#	−.56*	−.35	−.79
Post-error slowing	−.44#	.50*	−3.01**	−.13	.56**	−2.25**

[a]Pearson's correlation coefficient calculated within HC or ADHD group with age controlled.
[b]One-tailed *z*-score of the difference between the Fisher-transformed correlation coefficients.
#$p < .1$; *$p < .05$; **$p < .01$.

the early and late time windows respectively, and that these indices reveal impaired error processing in ADHD, arising from less efficient coordination of evoked brain activity. This is congruent with evidence of increased inter-trial variability in ADHD on behavioural (Castellanos et al., 2005; Johnson et al., 2007) and neural (Lazzaro et al., 1997) measures. Perhaps because of this variability, ITC appears more sensitive to abnormality in the ADHD group than the evoked power and ERP amplitude measures.

Relationships between behavioural measures and ITC

The HC group showed significant correlations between theta ITC, d-prime and RT variability, indicating that better performance (greater d-prime, low RT variability) was associated with greater phasic consistency in the neural response to errors, particularly in the late time window. Previous research has suggested not only that the ERN and Pe are generated by ACC (Mathalon et al., 2003) but also that connections between ACC and pre-frontal cortex (PFC) are important for guiding future behaviour on the basis of current performance (MacDonald, Cohen, Stenger, & Carter, 2000; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). Weaker error-related signals from ACC to PFC arising from less consistent phasic activation of the neural response might underlie the poorer inhibitory performance (lower d-prime) of the ADHD group and might account for the weaker, non-significant correlations between d-prime and ITC in this group. Another important finding is that although there was no group difference in post-error slowing, there were significant differences between the groups in the correlation between this index and ITC. In the HC group there were non-significant negative correlations whereas in the ADHD group there were significant positive correlations. This suggests that ITC is related to different aspects of performance in each group; to short-term adjustments immediately following an error in the ADHD group (post-error slowing) and to longer-term, more global adjustments in response style (d-prime, RT variability) in the HC group. Further work is needed to investigate relationships between behavioural and neural measures of error monitoring.

Study limitations and implications for future research

The sample sizes might have produced too little power to detect subtle differences in ERN amplitude between groups, although previous evidence of normal ERN amplitude in children with ADHD suggests that the finding is reliable. Secondly, although analyses were conducted to ensure that differences in gender ratio between the groups were unlikely to influence the results, further research is needed using gender-matched samples to ensure that this is the case. The results are applicable to DSM-IV ADHD combined subtype. It will also be important to determine whether the profile identified here is generalisable to the ADHD inattentive sub-type. Here, we were able to show that comorbidity with CD/ODD in the ADHD sample did not affect the results.

The go/no-go task employed here included a feedback signal on go trials when RT was longer than a specified time limit. Although the primary instruction given to participants was to be accurate on no-go trials, it is possible that the feedback signal decreased the motivational salience of no-go trials by encouraging participants to focus on go trials, potentially resulting in a smaller Pe. Given that the groups did not differ in median go RT, this is unlikely to account for the difference between groups reported here, but may be an issue for comparability with other studies which have not used a speed instruction. The Pe identified in the present study had a shorter mean latency and slightly more fronto-central topography than is typical, possibly because of the faster RTs of participants. In fact, the discrepancy in results between studies investigating ERN and Pe amplitude in ADHD indicates that issues such as paradigm design are likely to be important. For instance, recent studies using error awareness paradigms have described a frontal Pe occurring at around 100–150 ms (Endrass, Reuter, & Kathmann, 2007; O'Connell et al., 2009, 2007) which is topographically and functionally dissociable from the classic late Pe and which is reduced in adults with ADHD (O'Connell et al., 2009). An important aim for future research is to understand more fully the influence of factors such as task design and varying motivational salience on electrophysiological measures of error processing in ADHD; this will enable more accurate interpretation of abnormalities in this population and may help explain the discrepancy in results between studies.

Conclusions

In conclusion, this study identified significant abnormalities in electrophysiological measures of error processing in adolescents with ADHD and suggests that ITC is more sensitive than traditional ERP measures to error-processing abnormalities. These abnormalities may underlie the poor performance typically found in this population when carrying out tasks requiring efficient error-monitoring for successful performance such as the go/no-go task employed here and may also underlie the impulsive, error-prone behaviour observed clinically in ADHD.

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Key points

- Deficits in cognitive control, including error monitoring, may be one factor underlying hyperactive and impulsive behaviour in ADHD as young people with ADHD are less able to utilise performance feedback to regulate ongoing behaviour.
- Understanding the neural basis of error monitoring deficits can give important clues to the underlying physiology of ADHD.
- Abnormalities in electrophysiological indices of error processing, particularly increased variability in the phasic neural response to errors (inter trial coherence; ITC), provide novel insights into the neural correlates of these behavioural features.
- The work extends previous findings in children with ADHD to those in adolescence.
- The development of treatments that target deficient cognitive control, including error monitoring, in ADHD might ameliorate some aspects of symptomatology in this population.

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WORK 2

Chapter 4

Psychotomimetic and Cognitive Effects of Δ^9-Tetrahydrocannabinol in Laboratory Settings

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INTRODUCTION

A drug, in the context of human laboratory studies (HLS), is said to be psychotomimetic when its actions mimic signs and symptoms characteristic of psychosis, namely perceptual abnormalities (illusions and hallucinations), delusional beliefs and feelings, disorganization of thoughts and speech, and altered perceptions of self (such as dissociation). In addition, drugs may produce effects that resemble negative psychotic symptoms (apathy, anhedonia, alogia, asociality, avolition). Finally, drugs may also impair several aspects of cognition (memory, attention, executive function). Psychosis may be viewed as a core cluster of deficits in a number of functional domains, notably perception, cognition, and reward, and is observable in a range of acute (e.g., substance induced) and chronic (e.g., schizophrenia) conditions. Each condition may possess a unique admixture of additional deficits, for example in schizophrenia, where further, specific cognitive, affective, and functional impairments may also manifest. In this way, psychotomimetic drugs simulate core elements of psychosis in the absence of some of these collateral deficits, rather than a complete clinical picture.

This chapter will first discuss the properties of Δ^9-tetrahydrocannabinol (THC) and related cannabinoids used in HLS alongside key considerations when designing and interpreting these studies. Second, it will outline the psychotomimetic and cognitive effects in healthy humans and clinical populations that are relevant to schizophrenia, followed by factors that modulate those effects. Lastly, it will summarize biomarkers associated with these clinical effects with views toward future work (Fig. 1).

The Complex Connection between Cannabis and Schizophrenia. http://dx.doi.org/10.1016/B978-0-12-804791-0.00004-5

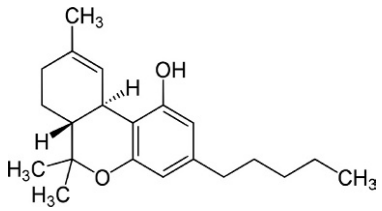

FIG. 1 Chemical structure of THC.

DESIGNING AND INTERPRETING HLS OF CANNABINOIDS

Properties of Cannabinoid Formulations Used in Laboratory Studies

THC, the principal psychoactive constituent of cannabis, is a partial agonist of type 1 (CB_1) and type 2 (CB_2) cannabinoid receptors. Various formulations of THC and related cannabinoids have been used in HLS in the United States (US): oral Dronabinol (THC), oral Nabilone (Cesamet), smoked National Institute of Drug Abuse (NIDA) standard cigarettes, and intravenous (IV) THC. Oral Dronabinol (Marinol) (10 mg capsule) is a US Food and Drug Administration (FDA)-approved synthetic form of THC that is typically used to treat anorexia in AIDS (acquired immunodeficiency syndrome) (and other wasting diseases), emesis in cancer patients undergoing chemotherapy, and chronic pain. Similarly, the 9-trans-ketocannabinoid Nabilone (Cesamet), a synthetic analog of THC, is indicated in the US for the treatment of chemotherapy-induced nausea. Of significance for investigators, these two oral agents are classed as schedule 3 (opposed to 1) substances due to their FDA-approved clinical indication, and thus have lesser regulatory requirements around use. NIDA manufactures and supplies standard cannabis cigarettes for medical research purposes in a range of THC potencies and more recently, cannabidiol (CBD) content. IV THC can be formulated for research use under the purview of the FDA as an investigational new drug, and stored under a schedule 1 license with the Drug Enforcement Administration (DEA). However, with the legalization of cannabis for medical and recreational purposes in the US, some states are in the process of making it possible to conduct research with cannabinoids, circumventing the schedule 1 license.

A key consideration in designing HLS is whether the pharmacokinetic and pharmacodynamic properties of the cannabinoid provide an adequate time window of neuropharmacological activity during which measurements can be made to answer the research question of interest. As noted by numerous studies, herbal marijuana contains over 400 chemicals belonging to 18 different classes (ElSohly et al., 2016; Mehmedic et al., 2010; Turner, Elsohly, & Boeren, 1980). The other lesser constituents that vary widely in concentration may have individual, interactive, or possibly entourage effects, which are not well understood and may confound the effects of the principle psychoactive

constituent, THC. The use of THC alone hence provides a more precise and controlled probe of the principal psychoactive effects of cannabis. However, it is important to recognize that THC may not accurately capture the full range of effects of herbal cannabis.

Another factor that determines the ecological validity of HLS is the degree to which the pharmacokinetic and pharmacodynamic properties of the administered THC parallel that of socially normative use. While smoking (and vaporizing) cannabis remains the most common method of consumption, the use of "edibles" or oral cannabinoid preparations has been steadily increasing in recent years. Homemade cannabis products (e.g., brownies and "cannabutter") are popular, and an array of commercial "edibles" including cannabis-infused drinks, candies, baked goods, and "dissolvables" (e.g., Cannastrips, Cannalixir) are widely available. Oral, IV, and vaporized cannabinoids have different pharmacodynamic and pharmacokinetic properties that provide unique opportunities for HLS to capture more ecologically valid scenarios of cannabis use.

THC is metabolized primarily in the liver by the cytochrome P450 (CYP) enzymes CYP2C9, CYP2C19, and CYP3A (Watanabe, Matsunaga, Yamamoto, Funae, & Yoshimura, 1995; Watanabe, Yamaori, Funahashi, Kimura, & Yamamoto, 2007). The primary metabolite, 11-hydroxy-delta-9-tetrahydrocannobinol (11-OH-THC), is at least as potent as THC, has a similar pharmacokinetic profile, and is thought to contribute significantly to the effects of THC (Perez-Reyes, Timmons, Lipton, Davis, & Wall, 1972). 11-OH-THC is further metabolized into the inactive metabolite 11-nor-9-carboxy-tetrahydrocannobinol (THC-COOH). It is THC-COOH that is detected in urine drug tests. Tissue distribution of THC and its major metabolites is dependent on its high lipophilicity (Garrett & Hunt, 1974; Hunt & Jones, 1980), causing it to distribute readily into highly vascularized tissue (Ho et al., 1970) and lipophilic tissue such as body fat (Garrett & Hunt, 1974; Johansson, Noren, Sjovall, & Halldin, 1989). THC also demonstrates significant plasma-protein binding (95%–99%) (Garrett & Hunt, 1974; Hunt & Jones, 1980). In plasma, low THC concentrations can be measured for extended periods after administration due to initial rapid redistribution and subsequent slow release ("reabsorption") from fatty tissue into the bloodstream (Hunt & Jones, 1980; Leuschner, Harvey, Bullingham, & Paton, 1986; Ohlsson et al., 1982); however, whether this release is of pharmacological relevance is not clear. Several models for the pharmacokinetics of THC have been published in studies with humans after IV (Lemberger, Tamarkin, Axelrod, & Kopin, 1971), oral (Wall, Sadler, Brine, Taylor, & Perez-Reyes, 1983), and intrapulmonary administration via smoking (Chiang & Barnett, 1984; Cocchetto, Owens, Perez-Reyes, DiGuiseppi, & Miller, 1981; Harder & Rietbrock, 1997) and using a vaporizer (Strougo et al., 2008).

Oral Administration

Orally consumed cannabinoids have a pharmacokinetic profile that is very different from inhaled or IV cannabinoids. The effects have a slower onset

of action but last much longer. Absorption is slower when cannabinoids are ingested, with lower, more-delayed peak THC concentrations (Agurell et al., 1986; Hampson, Grimaldi, Axelrod, & Wink, 1998; Harder & Rietbrock, 1997). Dose, route of administration, vehicle, and physiological factors such as absorption and rates of metabolism and excretion can influence drug concentrations in circulation. A high octanol/water partition coefficient (*P*) of THC (estimated to be between 6000 and $> 9 \times 10^6$) is thought to be responsible for its high rate of absorption. Perez-Reyes et al. examined the efficacy of five different vehicles (ethanol, sesame, glycocholate, emulsion of Tween-80, combination of ethanol and glycocholate) for oral administration of THC in gelatin capsules (Perez-Reyes et al., 1973). They found that glycocholate and sesame oil improved bioavailability although there was considerable variability in absorption and peak serum levels even within vehicles. Wall et al. have reported the bioavailability of oral THC to be 10%–20% (Wall et al., 1983). This complements a more accurate assessment of the oral bioavailability of THC by Ohlsson et al. based on gas chromatography/mass spectroscopy (GC/MS) experiments (Ohlsson et al., 1980). The peak THC concentration following ingestion of 20 mg of THC in a chocolate cookie occurred 1–5 h later and ranged from 4.4 to 11 ng/mL; the estimated oral bioavailability was 6%. Factors that may be responsible for the observed pharmacokinetics include variability in absorption, degradation of THC in the stomach, and significant first-pass metabolism to active 11-OH-THC as well as inactive metabolites in the liver.

In a study of 17 volunteers, following oral administration of a single capsule of Dronabinol (containing 10 mg of THC), mean peak plasma concentrations obtained 1–2 h later were as follows: THC = 3.8 ng/mL (range 1.1–12.7 ng/mL), 11-OH-THC = 3.4 ng/mL (range 1.2–5.6 ng/mL), and THC-COOH = 26 ng/mL (range 14–46 ng/mL) (Hampson et al., 1998). THC and 11-OH-THC concentrations were comparable, while consistently higher THC-COOH concentrations were observed. Also, interestingly, two THC peaks were frequently observed, possibly due to enterohepatic circulation. Compared to the smoked route, following ingestion of Dronabinol the onset of effects is delayed, peak THC concentrations are lower, and duration of pharmacodynamic effects is generally prolonged (Hampson et al., 1998; Ohlsson et al., 1980; Perez-Reyes et al., 1973; Plasse et al., 1991; Wall et al., 1983). Oral Nabilone has also been specifically shown to have a delayed onset of action (1–2 h) and long duration of effects (8–12 h) (Lemberger & Rowe, 1975). There are significant implications for recreational use as well as study dosing protocols and procedures. With the inhaled route, the dose can be titrated in real time. In contrast, given the delayed onset and longer duration of effects when administered orally, little can be done to alleviate negative effects (e.g., panic or psychosis), once they emerge. Furthermore, since the duration of effects is longer with oral consumption, individuals who are not familiar with the effects of cannabis may feel overwhelmed. Moreover, the inability to titrate effects with oral consumption may contribute to a greater sense of loss of control.

Intravenous Administration

The use of IV THC to probe the endocannabinoid system in the laboratory offers several advantages: it standardizes drug delivery and minimizes inter- and intraindividual variability in plasma THC levels, has rapid onset of action (10–15 min), and has a predictable peak (30–60 min), which enables researchers to capture time-locked psychophysiological measures relevant to the study. The pharmacokinetics of oral, inhaled (smoked), and IV cannabinoids were reviewed by Agurell et al. (1986) (Fig. 2). They reported that the plasma profiles of IV THC were comparable to those of smoked THC, although bioavailability was higher following smoking among heavy cannabis users versus light cannabis users. Ohlsson et al. compared the effects of oral, inhaled (smoked), and IV (5 mg over 2 min) THC in 11 healthy male volunteers. Compared to THC plasma levels after smoking and IV injection, THC plasma levels after oral doses were lower and irregular, indicating slow and erratic absorption (Ohlsson et al., 1980). As discussed, THC has low oral bioavailability due to degradation in the gut and extensive first-pass metabolism in the liver (Wall et al., 1983), which may account for these observations. Plasma levels of THC after smoking were similar to plasma levels after IV administration but were about 50% lower. Based on $AUC_{0–360\,min}$, systemic availability of THC after smoking and after oral administration were 18% ± 6% and 6% ± 3%, respectively. Wall et al. compared the pharmacokinetics of IV and oral THC in male and female volunteers (Wall et al., 1983). They found no significant differences in dynamic activity,

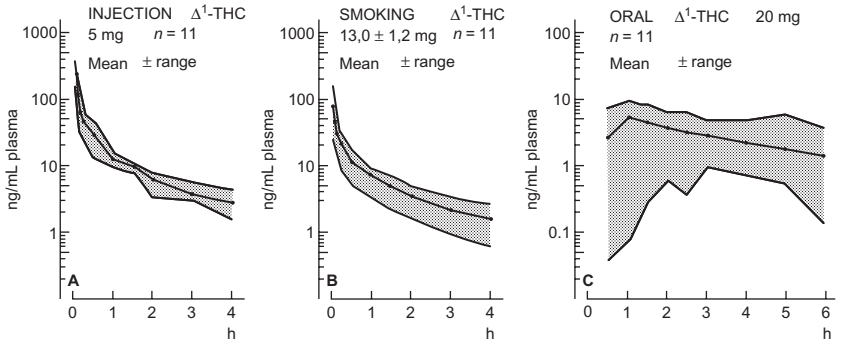

FIG. 2 Comparison of plasma Δ^9-tetrahydrocannabinol concentrations over time (in hours) following intravenous injection, smoking, and oral administration. *Reprinted with permission from Agurell, S., Halldin, M., Lindgren, J. E., Ohlsson, A., Widman, M., Gillespie, H., et al. (1986). Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man.* Pharmacological Reviews, 38, *21–43 and originally adapted from Ohlsson, A., Lindgren, J. E., Wahlen, A., Agurell, S., Hollister, L. E., & Gillespie, H. K. (1980). Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking.* Clinical Pharmacology and Therapeutics, 28, *409–416.*

metabolism, excretion, and kinetics between the two groups; however, the ratio of the concentrations of 11-OH-Δ-9-THC to Δ-9-THC in plasma after IV dosing was 1:10–20 versus 0.5–1:1 after oral dosing (Wall et al., 1983).

Smoking and Vaporization

Although smoking is a well-established route of administration, vaporization is a relatively new technology that allows for cannabinoids to be heated to a temperature below the point of combustion (which occurs at 230°C and above), where active cannabinoid vapors are rapidly formed while suppressing the production of pyrolytic toxic compounds and eliminating the harmful effects of secondhand smoke. In a number of studies, the vaporization of cannabis samples was systematically tested to show its advantages over smoking. A variety of vaporization and smoking devices (including water pipes) used for cannabis consumption have been systematically studied. When compared with direct smoking of cannabis, only vaporizers were found to be capable of achieving reductions in tar intake (McPartland & Pruitt, 1997). Furthermore, prior studies have shown that cannabis vaporization is more efficient than burning the plant material, due to reduced THC degradation (Abrams et al., 2007), and when compared to standard smoking, participants have shown preference for vaporization (Fischedick, Van Der Kooy, & Verpoorte, 2010). One study evaluated the Volcano vaporizer to test the variability of vaporizing parameters with respect to using pure cannabinoid preparations (THC and tetrahydrocannabinolic acid (THCA) diluted as ethanolic solutions) and cannabis plant material (200 mg at 12% THCA) (Hazekamp, Ruhaak, Zuurman, van Gerven, & Verpoorte, 2006). Their findings indicated that the vaporization of the cannabis plant material resulted in a maximum THC delivery of 29%, while the vaporization of pure THC resulted in a maximum THC delivery of about 53.9%, at a temperature of 226 ± 5°C. In addition, their results indicated that 30%–40% of inhaled THC was not absorbed by the lungs. In light of these findings, the difference in THC delivery yield between pure THC vaporization and cannabis plant material vaporization must be taken into account while deciding on an inhaled THC dose. The vaporization of 0.45 g of NIDA cannabis plant material (at a THC concentration of 1.7%) has been reported to produce a peak mean "high" effect of ~60, measured on a 0–100 visual analog scale (VAS) (Abrams et al., 2007). This effect is comparable to the effects of 2 mg of IV THC, which was reported to produce a peak "high" effect of ~50, measured on a 0–100 VAS (Borg, Gershon, & Alpert, 1975).

The rate at which THC enters the brain largely determines its effects. Thus, for smoking and vaporizer studies, the administration of each puff cycle, including the durations of inhalation, holding the smoke/vapor in lungs, and exhalation, has to be standardized by using a cued puff procedure such as the "Foltin Puff Procedure" (Fischman, Foltin, & Brady, 1988; Foltin, Fischman, & Byrne, 1988). In this procedure, participants are prompted to inhale for approximately

5 s, hold vapor in their lungs for approximately 10 s, and exhale and wait for approximately 45 s, after which the entire process is repeated.

A previous study comparing the administration of cannabis by vaporization to standard cannabis smoking found that subjective effects and plasma THC concentrations were generally similar in both administration techniques (Abrams et al., 2007). Their results indicated that the self-reported "high" did not differ during vaporization compared to smoking overall (6-h AUC), or at any observation point after consumption of cannabis. Furthermore, their findings indicated that the two modalities were not significantly different from one another at any of the three THC strengths (1.7%, 3.4%, and 6.8%) in the 6-h area under the plasma THC concentration-time curve (AUC), or for the peak THC plasma concentration measured at 2 min (Abrams et al., 2007).

Safety and Tolerability

The unpleasant psychoactive effects of THC include anxiety, panic, paranoia, and rarely, psychosis; all of these may be extremely distressing. However, the extent to which THC effects are perceived as unpleasant is context-dependent and can be reduced by preparing individuals in advance for the possible effects of THC. The acute physical effects of THC include motor incoordination, tremulousness, muscle weakness, hypo or hypertension, tachycardia, conjunctival injection, dry mouth, and increased appetite, which generally resolve spontaneously (Carbuto et al., 2012b). The estimated lethal dose of THC is 30 mg/kg (2100 mg in a 70-kg individual), which is several thousand times the amount of THC in a standard cannabis joint. It should be noted that no fatalities have been reported with cannabis overdose.

THC has been administered in very large oral doses (50–712 mg) and modest IV doses (1–10 mg) to cannabis users without any serious adverse events (Hollister, 1986). D'Souza et al. have conducted a series of studies with varying doses of THC (1.75–5 mg) administered over varying times (2–20 min) to several groups of subjects ($n > 400$) including cannabis users, nonusers, and patients with schizophrenia (D'Souza et al., 2005), and have shown that it was safe and well tolerated (Ranganathan & D'Souza, 2006b).

There are no major differences between the type of unpleasant behavioral and acute physical effects induced by IV THC, smoked cannabis, and oral Dronabinol. Hypotension may be more likely to be observed with IV THC (D'Souza: unpublished observations). However, as discussed earlier, the slower onset and longer duration of effects of oral THC may have implications if adverse effects are experienced during a study.

The majority of the studies that make up the existing literature on the effects of cannabis consumption use standard smoking as their drug administration method, which exposes subjects to a variety of toxins produced by the combustion of the cannabis plant material. Previous studies that investigated the smoke harm reduction associated with vaporization of cannabis showed that the

vaporizers produced qualitative reduction in carbon monoxide and particulates, and complete elimination of benzene, toluene, and naphthalene, which are three toxic hydrocarbons produced by standard cannabis smoking. Another study that investigated vaporization as a smokeless means of delivery of inhaled *Cannabis sativa* reported no adverse events and indicated that vaporization of cannabis is a safe and effective mode of delivery of cannabinoids (Abrams et al., 2007).

Many recent studies that have investigated the administration of vaporized THC point to the conclusion that vaporized THC administration may be a safer method, producing cognitive and psychotropic effects similar to oral and IV THC, with no adverse events reported. In terms of somatic effects produced by vaporization, previous studies using THC dissolved in an ethanolic solution reported side effects such as slight irritation of the throat and upper respiratory tract as well as mild coughing (Hazekamp et al., 2006; Naef, Russmann, Petersen-Felix, & Brenneisen, 2004). These side effects were reversible within 30 min of finishing the inhalation. One study found that these complaints were also observed during inhalation of placebo and were attributed to effects of residual ethanol. No serious adverse events were reported.

HLS in clinical populations have been controversial due to theoretical safety concerns and ethical considerations. However, it has been demonstrated that the administration of THC in laboratory contexts induces symptoms only transiently and has no effect on the participants' desire to use cannabis for up to a year after study participation (Carbuto et al., 2012a). One study reported an event of hospitalization for exacerbation of hypertension, which the subject failed to disclose at the time of screening. As with healthy controls, nausea and dizziness were the common minor side effects at the higher end of IV dosing. Study participation did not impact the course of illness or cannabis use in patients with schizophrenia in a 6-month follow-up study (Carbuto et al., 2012a).

Some Considerations on Study Design

Multiple lines of evidence have indicated a role for the endocannabinoid system in the pathophysiology of schizophrenia (Bossong, Jansma, Bhattacharyya, & Ramsey, 2014; Gupta, Cahill, Ranganathan, & Correll, 2014). Therefore, in addition to inducing nonphysiological states in healthy individuals, laboratory-based THC challenge studies can be used to probe abnormalities in the endocannabinoid systems of individuals with schizophrenia in order to identify markers of disease. Further, conducting similar studies in individuals at genetic risk for disease but without psychosis may help elucidate pathophysiology without confounds such as collateral effects of the illness and the presence of antipsychotic medications. THC challenge studies in individuals with different degrees of genetic and clinical risk also form a paradigm for probing gene–gene interaction related to the role of cannabis in the pathophysiology of schizophrenia. THC challenges in individuals with a genetic diathesis for psychosis may also serve as a test for the extent of their vulnerability for psychosis and may assist in identification

of at-risk individuals who might benefit from early interventions to prevent the development of schizophrenia (Gupta, Ranganathan, & D'Souza, 2016b).

It is recognized that individuals with psychotic disorders and comorbid cannabis use disorder have a significantly worse prognosis than those with psychotic disorders alone (Swendsen, Ben-Zeev, & Granholm, 2011). Their cannabis use leads to symptom exacerbation (Buckley, Miller, Lehrer, & Castle, 2009), an increased likelihood of psychotic relapse, and an overall worse global functioning (Zammit et al., 2008). However, subjective reports from some psychotic individuals who use cannabis indicate that they experience a relief of symptoms when they use cannabis (Schofield et al., 2006). Further, a small case series of the use of dronabinol in the treatment of schizophrenia has indicated some efficacy (Schwarcz, Karajgi, & McCarthy, 2009). In the situation where subjective reports contradict large-scale empirical data, a controlled laboratory-based measurement of the effects of THC on individuals with psychosis is of immense value. Studies of the effects of THC in schizophrenia have helped clarify these contradictory findings. Further, these challenge studies can serve as a paradigm to test specific treatments for comorbid cannabis use and schizophrenia, targeting either the cognitive or the subjective euphoric effects of cannabis (similar to the use of naltrexone in alcohol or opioid dependence).

The acute administration of cannabinoids in tightly controlled laboratory settings allows for both a clearer inference of causality of effects and a more detailed characterization of those effects. In the laboratory, the high variability in cannabinoid content (specifically THC and CBD) of street cannabis products available and the manner and route of consumption (greatly affecting bioavailability) can be controlled, facilitating more precise delineation of dose-response relationships. Similarly, the biological, psychological, and the social context of cannabinoid administration can be better described and controlled through a careful selection and characterization of subjects, the enforcement of study restrictions, and the rigorous standardization of the study environment and procedures. Furthermore, given recent evidence questioning the validity of self-reported cannabinoid effects, HLS allow for the ongoing investigation of a potential dissociation between subjective and objective effects. Lastly, although HLS have direct inferential value in studying the nature of acute, intoxication-related cannabinoid-induced psychosis, the degree to which psychotomimesis reflects any other type of clinical psychosis remains subject to debate. Nevertheless, the induction of these transient psychosis-like (and cognitive) effects in healthy controls allows for the isolation of "state" (opposed to "trait") features and biomarkers that are, at the very least, phenomenologically relevant to psychosis. This differentiation of *state* and *trait* may further facilitate the discovery of potential overlaps in the seemingly heterogeneous pathoetiologies of psychotic states.

HLS with cannabinoids are not without limitations. Tight inclusion and exclusion criteria, operationalized cannabinoid administration, and the inevitable influence of the laboratory environment on effects experienced constrain the

generalizability and/or limit the interpretation of this type of study. Subjects may self-select due to past positive or negative associations with cannabis and/or laboratory-based research in general. Most notably, those who have experienced past adverse effects from cannabinoids may be unlikely to volunteer for such studies. Despite providing a useful laboratory model of psychosis in humans, HLS using cannabinoids are unlikely to ever adequately replicate the full range of deficits observed in psychotic disorders and therefore can provide only a restricted, though penetrating, view. They remain a vital complement to epidemiological and other more ecologically valid study designs.

EFFECTS OF Δ^9-TETRAHYDROCANNABINOL IN HUMAN LABORATORY STUDIES

Effects in Healthy Individuals

Experimental studies have shown that the acute effects of cannabinoids resemble, in an attenuated way, some core phenomenology of psychosis and schizophrenia; these effects have been captured using standardized scales such as the Positive and Negative Symptom Scale for Schizophrenia (PANSS) (Fig. 3), Clinician Administered Dissociative Symptoms Scale (CADSS), Psychotomimetic States Inventory (PSI), and the Brief Psychiatric Rating Scale (BPRS). These psychotomimetic effects include positive- and disorganization-like symptoms such as suspiciousness, paranoid and grandiose delusions, perceptual alterations, conceptual disorganization, and fragmented thinking. Furthermore, they also include negative-like symptoms such as blunted affect, reduced rapport, emotional withdrawal, psychomotor retardation, and lack of spontaneity (D'Souza et al., 2004; Kleinloog et al., 2012b; Liem-Moolenaar et al., 2010; Morrison & Stone, 2011; Morrison et al., 2009), which are not an effect of the sedating and cataleptic effects of THC (Morrison & Stone, 2011). In addition, cannabinoids have been shown to induce dissociative symptoms

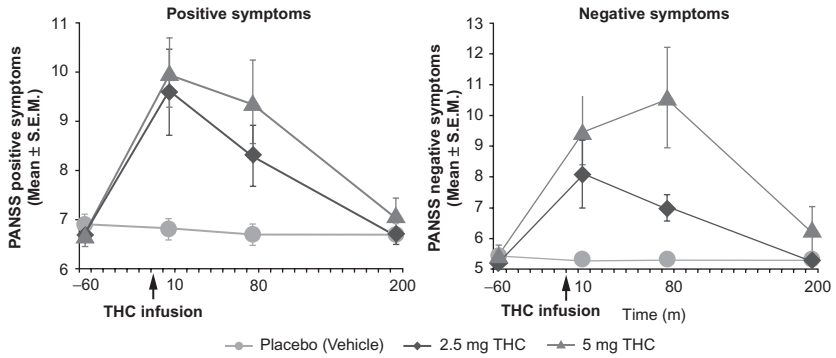

FIG. 3 Comparison of pharmacokinetics of IV smoked and oral THC.

TABLE 1 The Quality of Psychotomimetic Effects Reported by Healthy Individuals Following Intravenous Infusion of 5 or 2.5 mg of THC as It Relates to Typical Signs and Symptoms of Schizophrenia

Subject Quote	Symptom
I thought you could read my mind, that's why I didn't answer	Suspiciousness/paranoia
I thought you all were trying to trick me by changing the rules of the tests to make me fail	
I could hear someone on typing on the computer… and I thoughts you all were trying to program me	
I thought you all were giving me THC through the BP machines and the sheets	
I couldn't keep track of my thoughts… they'd suddenly disappear	Formal thought disorder
It seemed as if all the questions were coming to me at once… everything was happening in staccato	
My thoughts were fragmented… the past, present and future all seemed to be happening at once	
I felt I could see into the future… I thoughts I was God	Grandiosity
The AC that I couldn't hear before suddenly became deafening	Perceptual abnormalities
I thought I could hear the dripping of the iv and it was louder than your voice	

Reprinted with permission from D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. T., et al. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis. *Neuropsychopharmacology*, *29*, 1558–1572.

such as depersonalization, derealization, altered body perception, feelings of unreality, and extreme slowing of time (D'Souza et al., 2004; Kleinloog et al., 2012b; Liem-Moolenaar et al., 2010; Morrison & Stone, 2011; Morrison et al., 2009). Table 1, adapted from D'Souza 2004, illustrates the quality of a range of psychotomimetic symptoms expressed on a retrospective report of peak THC effects (D'Souza et al., 2004).

More than 50 HLS have been published since the 1970s featuring THC as the predominant interventional agent, as summarized in Table 2.

The types of psychotomimetic effects of cannabinoids have been shown to be consistent across a range of doses and routes of administration, such as smoked cannabis, oral cannabis extract/THC (5–20 mg), IV THC (~0.015–0.06 mg/kg), and inhaled vaporized THC (Bhattacharyya, Crippa, et al., 2012c; D'Souza et al., 2004; Englund et al., 2013a; Kaufmann et al., 2010; Martin-Santos et al., 2012a;

TABLE 2 A Summary of HLS Featuring THC as the Predominant Interventional Agent—Psychosis-Relevant, Cognitive, and Physiological Effects

Author(s)	Year	Subjects	THC (And Other Drugs) Dose and Route	Psychosis-Relevant Effects	Cognitive Effects	Physiological Measures
Bossong et al. (2015)	2015	19 healthy volunteers with history of previous exposure	2 studies: 10 mg of dronabinol PO and 8 mg of THC inhaled using vaporizer	N/A	N/A	PET: Significant reduction in tracer binding to D2/D3 receptors in the limbic striatum
Bhattacharyya et al. (2015)	2015	15 healthy males (same population as Bhattacharyya et al., 2009)	10 mg THC-PO 600 mg CBD-PO	N/A	N/A	fMRI: opposite effects of THC and CBD on functional connectivity between dorsal striatum, PFC and hippocampus
Bossong et al. (2013)	2013	14 healthy males	6 mg followed for 3 times by1 mg of THC—inhalation using vaporizer	SUBJ: ↑ feelings of high, internal perception, external perception. ↓ calmness, alertness and contentedness	N/A	fMRI: Differential activation of different brain regions between fearful faces and happy faces.
Atakan et al. (2013)	2013	21 healthy males	10 mg of THC-PO	PANSS: ↑ positive, negative, general. SUBJ: ↓ tranquility ↑ anxiety ↑ intoxication	go/no-go task: ↑ inhibition errors	fMRI: THC versus plac = ↓ left PHG, MTG, STG, while ↑ activation of right MTG in transiently psychotic group

Sewell et al. (2013a)	2013	44 subjects [34 nonusers (27 males) and 10 chronic users (6 males)]	0.015–0.05 mg/kg of THC-IV	SUBJ: Nonusers: temporal overestimation at medium and high doses, and underproduction at all doses Chronic users: effects were blunted at all doses	N/A	N/A
Kuepper et al. (2013b)	2013	9 healthy cannabis users, 8 patients with psychotic disorder and 7 first-degree relatives	8 mg of THC—inhalation through vaporizer	SUBJ: ↑ feeling high, external perception, internal perception	N/A	PET: No dopamine release in the control group THC induced dopamine release in both the patients and relatives, most pronounced in caudate nucleus
Englund et al. (2013b)	2013	48 (22 receiving CBD, 26 receiving placebo)	1.5 mg THC-IV 600 mg CBD-PO versus placebo	PANSS: less likely ↑ in positive score with CBD SSPS: less in CBD versus placebo	HVLT-R: poorer scores in the placebo group compared to CBD	N/A
Bhattacharyya, Atakan, et al. (2012b)	2012	36 healthy males	10 mg of THC-PO	PANSS: 9 repeat carriers of DAT1 gene is associated with more psychotic symptoms induced by THC GG of AKT1 has even higher	N/A	fMRI: GG/9 carriers have attenuated activation of striatum and midbrain, which was correlated with severity of psychotic symptoms

Continued

TABLE 2 A Summary of HLS Featuring THC as the Predominant Interventional Agent—Psychosis-Relevant, Cognitive, and Physiological Effects—cont'd

Author(s)	Year	Subjects	THC (And Other Drugs) Dose and Route	Psychosis-Relevant Effects	Cognitive Effects	Physiological Measures
Ranganathan et al. (2012) [7]	2012	30 volunteers (26 males) (7 regular users)	0.0286 mg/kg of THC-IV with 25 mg Naltrexone PO	PANSS: ↑ positive, negative and general subscores (no change with naltrexone) CADS: ↑ perceptual alterations (no change with naltrexone) SUBJ: ↑ high, anxious, tired, calm (no change with naltrexone)	HVLT: impaired immediate and delayed recall (no change with naltrexone)	N/A
Kleinloog et al. (2012a)	2012	49 healthy men with mild exposure to cannabis	2, 4, and 6 mg of THC—inhalation by vaporizer with 10 mg of olanzapine PO versus two 15 mg of diphenhydramine PO	PANSS:↑ positive (which was reduced by olanzapine, but not with diphenhydramine) ↑ general SUBJ: ↑ calmness ↓ alertness	VVLT: ↓ delayed recall Stroop test: no effect	N/A
D'Souza et al. (2012a)	2012	26 healthy volunteers (17 males)	0.015 mg/kg and 0.03 mg/kg of THC- IV	PANSS: ↑ positive, negative, and general CADSS: ↑ SUBJ: ↑ high	N/A	EEG: Reduced amplitude of novelty P300a and target P300b. No change in latency.

Martin-Santos et al. (2012b)	2012	16 healthy males	10 mg THC-PO 600 mg CBD-PO	Positive psychotic symptoms with THC, none with CBD or placebo SUBJ: ↑ anxiety, dysphoria, sedation with THC, not with CBD or placebo	N/A	N/A
Bhattacharyya, Atakan, Martin-Santos, Crippa, and McGuire (2012a)	2012	15 healthy men with minimum history of previous cannabis use	10 mg THC-PO 600 mg CBD-PO	PANSS: ↑ positive with THC, none with CBD or placebo	N/A	fMRI (visual oddball detection): THC attenuated activation of right caudate, which was inversely correlated with severity of psychotic symptoms CBD resulted in opposite effects to THC on task-related changes
Morrison et al. (2011)	2011	16 healthy volunteers (7 males)	1.25 mg of THC-IV	PANSS: ↑ positive, negative, and general	N-back task: slower response times	EEG: ↓ bifrontal coherence in theta and alpha bands
Morrison and Stone (2011)	2011	19 healthy males	2.5 mg of THC-IV	PANSS negative: ↑ CAPE negative: ↑ SUBJ: no relationship between increased CAPE negative scores and self-rated sedation	N/A	N/A
Barkus et al. (2011)	2011	9 healthy males	2.5 mg of Dronabinol-IV	PANSS: ↑ positive, general, and negative	N/A	SPECT: IV THC didn't significantly increase DA release in the caudate or putamen

Continued

TABLE 2 A Summary of HLS Featuring THC as the Predominant Interventional Agent—Psychosis-Relevant, Cognitive, and Physiological Effects—cont'd

Author(s)	Year	Subjects	THC (And Other Drugs) Dose and Route	Psychosis-Relevant Effects	Cognitive Effects	Physiological Measures
Winton-Brown et al. (2011)	2011	14 healthy males	10 mg THC-PO 600 mg CBD-PO	PANSS: ↑ positive with THC, none with CBD SUBJ: ↑ sedation, intoxication, anxiety with THC, none with CBD	N/A	fMRI: THC attenuates, while CBD activates temporal areas related to processing of information
Stadelmann et al. (2011)	2011	20 healthy volunteers (10 males)	10 mg THC-PO Cannabis extract: 10 mg of THC and 5.4 mg of CBD-PO	N/A	N/A	EEG: P300: >10/>10 genotype of CNR1 gene is associated with significant decrease of P300 amplitude and significant prolongation of P300 latency with THC but not cannabis Extract For pure THC, the higher the number of AAT repeats, the smaller amplitude of P300 and the longer the latency
Kaufmann et al. (2010)	2010	15 healthy females	20 mg of THC as PO cannabis extract versus 5 mg of diazepam as an active placebo	BPRS score: ↑ SUBJ: ↑ fatigue, drowsiness, dizziness, "feeling high"	N/A	N/A

Liem-Moolenaar et al. (2010)	2010	35 healthy male volunteers with mild cannabis use	2, 4, and 6 mg of THC—intrapulmonary by vaporizer with 3 mg Haloperidol PO versus Placebo	PANSS:↑ positive (reduced by haloperidol) ↑ general SUBJ: ↑ external, internal perception, feeling high ↓ alertness (no effect of haloperidol)	Stroop test: ↓ Immediate and delayed word recall: impaired (immediate recall corrected by haloperidol)	EEG: ↑ alpha power in Fz-Cz (no effect of haloperidol)
Stone et al. (2010)	2010	16 healthy volunteers (9 females)	1.25 mg of THC-IV	SUBJ: Impairment of time perception, delay between thinking and speaking, impaired attention, concentration	Slowed tap time (related to impaired concentration)	N/A
Bocker et al. (2010)	2010	16 participants	29.3, 49.1, or 69.4 mg of THC-smoking	N/A	↑ reaction time and number of errors	EEG: resting: ↓ theta, ↑ beta power (Memory effect and theta changes are correlated)
Bhattacharyya et al. (2010)	2010	fMRI expt: Fifteen healthy men with minimal earlier exposure to cannabis (from Bhattacharyya et al., 2009)	fMRI expt: 10 mg THC-PO fMRI expt: 600 mg CBD-PO	N/A	N/A	fMRI: opposite effects of THC and CBD on striatum, hippocampus, amygdala, superior temporal cortex, occipital cortex
Bhattacharyya et al. (2010)	2010	Behavioral expt: 6 healthy volunteers	Behavioral expt: 1.25 mg THC Behavioral expt: 5 mg CBD-PO	PANSS: ↑ positive with THC, not with CBD	N/A	N/A

Continued

TABLE 2 A Summary of HLS Featuring THC as the Predominant Interventional Agent—Psychosis-Relevant, Cognitive, and Physiological Effects—cont'd

Author(s)	Year	Subjects	THC (And Other Drugs) Dose and Route	Psychosis-Relevant Effects	Cognitive Effects	Physiological Measures
Morrison et al. (2009)	2009	22 healthy males	2.5 mg of Dronabinol-IV	PANSS: ↑ positive CAPE: ↑ SUBJ: UMACL: ↓ hedonic tone—↓ energetic arousal—↑ tense arousal	RAVLT: ↓ immediate recall no change on Verbal Fluency Baddeley Reasoning Task: ↓ performance	N/A
Bhattacharyya et al. (2009)	2009	15 healthy males	10 mg THC-PO 600 mg CBD-PO	PANSS: ↑ positive, negative, general with THC, none with CBD SUBJ: ↑ sedation, intoxication, anxiety with THC, none with CBD	N/A	fMRI: THC augments activation of PHG and attenuated ventrostriatal activation—correlated with psychotic symptoms—no changes with CBD
Fusar-Poli et al. (2009)	2009	15 healthy males	10 mg THC-PO 600 mg CBD-PO	PANSS: ↑ positive, negative, and general with THC, not with CBD SUBJ: Skin-conductance responses: fluctuations in response to fearful faces ↑ with THC and ↓ with CBD ↑ Anxiety with THC, not with CBD	N/A	fMRI (showing faces): CBD reduced amygdala and anterior and posterior cingulate in response to fearful faces (correlated with decreased skin-conductance responses). THC modulated activation in frontal and parietal areas

D'Souza, Ranganathan, et al. (2008b)	2008	22 controls (14 males); 30 frequent users (21 males)	2.5 and 5 mg of THC-IV	PANSS: ↑ total score (less with frequent users than with controls) CADSS: ↑ (smaller effect in frequent users) SUBJ: Anxiety: ↑ (smaller increase in frequent users) Calm and relaxed: ↓	HVLT: immediate and delayed recall: impaired (both showed smaller effect in frequent users) ↑ number of intrusions and false positive responses Attention: ↑ omission and commission errors	N/A
D'Souza, Braley, et al. (2008d)	2008	17 healthy subjects and 11 frequent users of cannabis	0.0286 mg/kg of THC-IV with Haloperidol 0.057 mg/kg PO versus placebo	PANSS: ↑ total and positive CADSS: ↑ subjective and objective SUBJ: ↑ high, tired	Impaired verbal recall and attention	N/A
Borgwardt et al. (2008)	2008	15 healthy males	10 mg THC-PO 600 mg CBD-PO	PANSS: ↑ positive with THC, no changes with CBD. SUBJ: ↑ sedation, intoxication and anxiety with THC, no sig. effects with CBD		fMRI: THC reduced activation in right inferior frontal and anterior cingulate cortex—CBD deactivated left temporal cortex and insula
Roser et al. (2008)	2008	20 healthy volunteers (10 males)	10 mg THC-PO Cannabis extract: 10 mg of THC, 5.4 mg of CBD-PO	N/A	N/A	EEG: auditory evoked P300: significant reduction of P300 amplitude at midline frontal, central, and parietal electrodes—not corrected by CBD

Continued

TABLE 2 A Summary of HLS Featuring THC as the Predominant Interventional Agent—Psychosis-Relevant, Cognitive, and Physiological Effects—cont'd

Author(s)	Year	Subjects	THC (And Other Drugs) Dose and Route	Psychosis-Relevant Effects	Cognitive Effects	Physiological Measures
Juckel et al. (2007)	2007	22 healthy volunteers (11 males)	10 mg THC-PO Cannabis extract: 10 mg of THC, 5.4 mg of CBD-PO	N/A	N/A	EEG: auditory evoked MMN: MMN amplitudes were larger with cannabis extract but not with pure THC (in central electrodes)
Koethe et al. (2006)	2006	16 antipsychotic naïve schizophrenia or schizophreniform patients (13 males), 16 prodromal state individuals (11 males), 16 healthy controls (9 males), 16 healthy males receiving Dronabinol	120 μg/kg of Dronabinol-PO	BPRS: ↑ among patients, prodromal state, healthy controls receiving Dronabinol than healthy controls (with patients having highest scores) BDII: impaired among patients, prodromal state individuals, healthy controls receiving Dronabinol—no difference between them	N/A	N/A

Henquet et al. (2006c)	2006	30 patients with a psychotic disorder, 12 relatives of patients with a psychotic disorder, and 32 healthy controls	300 mg THC/kg body weight in tobacco cigarettes in the exposure condition, or 0 mg THC/kg body weight in tobacco cigarettes	CAPE: Carriers of the Val allele were most sensitive to the induced psychotic experiences on the condition of higher psychosis liability	Visual Verbal learning test—Abstract Visual Pattern Learning—Continuous Performance Test—Stroop Color-Word test—Digit Symbol Substitution Test: Sensitivity to memory and attention impairments is more among carriers of the Val allele	N/A
D'Souza et al. (2005)	2005	13 stable, antipsychotic-treated patients	2.5 and 5 mg of THC-IV	PANSS: ↑ positive, negative, general CADSS: ↑ clinician and participant rated	HVLT: impaired immediate, delayed recall	N/A

Continued

TABLE 2 A Summary of HLS Featuring THC as the Predominant Interventional Agent—Psychosis-Relevant, Cognitive, and Physiological Effects—cont'd

Author(s)	Year	Subjects	THC (And Other Drugs) Dose and Route	Psychosis-Relevant Effects	Cognitive Effects	Physiological Measures
Ilan et al. (2005)	2005	23 healthy users (12 men) (22 of users used for EEG and ERP analysis)	Low (1.8%) or high (3.6%)-smoking Low (between 0.1 and 0.4%) or high (more than 1 %) CBD-smoking Cannabichromene (CBC) containing cigarettes: Low (between 0.1% and 0.2%) or high (more than 5%) Cigarettes were combination of: Low THC, low CBD, high CBC High THC, low CBD, high CBC Low THC, high CBD, low CBC Low THC, high CBD, high CBC	N/A	Word presentation, working memory and word recognition tasks: reduced performance with THC—changing doses of CBD and CBC did not change effects	EEG: THC lowered amplitude of ERP and reduced EEG power—effects were not dose dependent—changing doses of CBD and CBC didn't change effects

D'Souza et al. (2004)	2004	22 healthy volunteers	2.5 and 5 mg of THC-IV	PANSS: ↑ positive, negative, general CADSS: ↑ clinician and participant rated SUBJ: ↑ anxiety, tiredness ↓ calmness	HVLT: impaired immediate, delayed recall	N/A
McDonald, Schleifer, Richards, and de Wit (2003b)	2003	37 men and women	7.5 and 15 mg of THC-PO	SUBJ: THC ↑ estimates of the duration of short intervals while not affecting estimates of longer intervals ↑ stop reaction time No effect on go reaction time, go/no-go task	HVLT, digit span forward: no effect Digit span backward: impaired	N/A
Hart et al. (2001)	2001	18 healthy volunteers (10 males), averaging 24 marijuana cigarettes per week	1.8%, 3.9% of THC-smoking	SUBJ: ↑ confused, mellow, high	MicroCog test battery: ↑ premature responses—↑ time needed to finish tasks—did not affect accuracy on cognitive flexibility, mental calculation and reasoning Impaired immediate recall	N/A

Continued

TABLE 2 A Summary of HLS Featuring THC as the Predominant Interventional Agent—Psychosis-Relevant, Cognitive, and Physiological Effects—cont'd

Author(s)	Year	Subjects	THC (And Other Drugs) Dose and Route	Psychosis-Relevant Effects	Cognitive Effects	Physiological Measures
Leweke et al. (2000)	2000	9 healthy males	1 mg of Nabilone-PO 200 mg CBD-PO	BDII: marked impairment after nabilone alone—less impairment after combined nabilone and CBD—no effect after CBD alone	N/A	N/A
Mathew et al. (1998)	1998	46 subjects (22 males)—mean marijuana use: 147 ± 165.2 "joints" per year	0.15 mg/min versus 0.25 mg/min (for 20 min) of THC-IV	N/A	N/A	PET: individuals who had reduced cerebellar blood flow after THC experienced significant alteration in time perception
Leweke et al. (1998)	1998	19 healthy volunteers	10 mg of Dronabinol-PO	N/A	↓ accuracy of classification of emotionality of words	ERP: ↑ of amplitude of ERP in response to the positive words when they are presented for the second time
Emrich et al. (1991)	1991	7 healthy subjects	3–4 mg/kg of cannabis resin-PO	BDII: impaired	N/A	N/A
Heishman et al. (1990)	1990	3 experienced users	0, 1, or 2 marijuana cigarettes (each containing 2.57% of THC)	N/A	Serial addition/subtraction and digit recall tasks: impaired Impairment lasted for 24 h	N/A

Marks and MacAvoy (1989)	1989	6 experienced users and 6 nonusers (equal male and female ratios)	0, 2.6, and 5.2 mg of THC-smoking versus 1.19 mL/kg and 2.38 mL/kg drink containing 42% w/v ethanol	N/A	Both THC and alcohol impaired signal detection (more pronounced for peripheral signals, with users being less impaired than nonusers)	N/A
Hooker and Jones (1987)	1987	12 males (variable marijuana use)	10.7 ± 0.6 mg of THC-smoking	N/A	Delayed free recall: more errors Immediate, sustained attention, controlled retrieval from semantic memory, speed of reading, naming colors: not affected Stroop test: ↑ interference	N/A
Hicks et al. (1984)	1984	Experiment 1: 4 healthy males Experiment 2: 6 experienced users (3 males)	1.29 or 4.61% of THC-smoking (cigarettes were ~9.23 mg) with 0.2 mg of atropine sulfate-IV Smoking cigarettes containing THC	SUBJ: Experiment 1: ↑ subjective time rate and effect not related to blocking cholinergic effect Experiment 2: Increased subjective time rate is evident as time is passing	N/A	N/A

Continued

TABLE 2 A Summary of HLS Featuring THC as the Predominant Interventional Agent—Psychosis-Relevant, Cognitive, and Physiological Effects—cont'd

Author(s)	Year	Subjects	THC (And Other Drugs) Dose and Route	Psychosis-Relevant Effects	Cognitive Effects	Physiological Measures
Miller et al. (1977)	1977	2 groups of 17 male volunteers	14 mg of THC-smoking	N/A	Immediate and final free recall: ↓ Long term retention: not affected	N/A
Melges et al. (1974)	1974	6 healthy males	20 mg of THC containing cigarettes smoked over 10 (fast) or 45 min (slow) versus 120 mL of 95% alcohol drink as active placebo [consumed over 10 min (fast) or 45 min (slow)]	Inventories: ↑ temporal disorganization, delusional-like ideations, amplification, desynchronization ↑ depersonalization	↑ tracking difficulties	N/A
Tinklenberg et al. (1972)	1972	15 healthy males users	0.35 mg/kg of THC-PO versus 0.7 mL/kg of 95% ethanol	SUBJ: Underproduction of time intervals	N/A	(reported in the study (Kopell, Tinklenberg, & Hollister, 1972))
Kopell et al. (1972)	1972	12 healthy males users	0.35 mg/kg of THC-PO versus 0.7 mL/kg of 95% ethanol	N/A	N/A	EEG: amplitude of contingent negative variation ↑ with THC, ↓ with alcohol

THC: Δ-9-tetrahydrocannabinoid; Sxs: symptoms; PHG: parahippocampal gyrus; MTG: middle temporal gyrus; STG: superior temporal gyrus; RAVLT: Rey Auditory Verbal Learning Task; UMACL: University of Wales Institute of Science and Technology Mood Adjective Checklist; BDII: Binocular depth inversion illusion test; HVLT: Hopkins Verbal Learning Test; SUBJ, subjective effects.

Morrison & Stone, 2011; Morrison et al., 2009). However, the intensity of effects has also been shown to be dose dependent and to have distinct time courses depending on the route of administration (D'Souza et al., 2004; Kleinloog et al., 2012b; Liem-Moolenaar et al., 2010; Morrison & Stone, 2011; Morrison et al., 2009).

In a first study of its kind, D'Souza et al. (2004) administered two doses of IV THC (2.5 and 5 mg) to healthy adults using a double-blind, randomized, placebo-controlled, crossover design (D'Souza et al., 2004). The study found that THC induced perceptual alterations, a wide range of psychotomimetic symptoms, mood symptoms such as euphoria and anxiety, and cognitive deficits affecting attention and working and verbal memory. These findings were first replicated by Morrison et al. (2009) using a lower dose of IV THC (2.5 mg), and then by a number of researchers using a range of doses (1.25–3.5 mg) and infusion times (10–20 min) (Bhattacharyya et al., 2009, 2010, 2015; Bhattacharyya, Crippa, et al., 2012d; D'Souza, Braley, et al., 2008; D'Souza et al., 2012a; Freeman et al., 2015).

Nabilone, a synthetic analog of THC (Leweke, Schneider, Radwan, Schmidt, & Emrich, 2000; Leweke, Schneider, Thies, Munte, & Emrich, 1999), and Dronabinol, a synthetic isomer of THC (Koethe et al., 2006), have been shown to share a similar profile of effects with THC. In addition, in healthy controls, they have been found to induce deficits in the binocular depth inversion illusion task, a potential surrogate marker for psychosis present in patients with acute paranoid schizophrenia and schizophreniform psychosis (Koethe et al., 2006; Leweke et al., 1999, 2000).

As summarized in Table 2, in healthy humans, cannabinoids have also been shown to acutely induce a range of transient, dose-related deficits in cognitive processes, such as verbal learning, short-term memory, working memory, executive function, abstract thinking, decision-making, and attention (Hart, van Gorp, Haney, Foltin, & Fischman, 2001; Heishman, Huestis, Henningfield, & Cone, 1990; Hooker & Jones, 1987; Leweke et al., 1998; Marks & MacAvoy, 1989; Miller, McFarland, Cornett, & Brightwell, 1977; Ranganathan & D'Souza, 2006a). These findings have been consistent with the acute effects of cannabinoids observed in nonhuman primates and rodents (for a review, see Lichtman, Varvel, & Martin, 2002; Wilson & Nicoll, 2002). Importantly, the profile of cognitive deficits induced by cannabinoids is similar to that observed in schizophrenia (Heinrichs & Zakzanis, 1998): in both cases, working and verbal memory are the most affected domains (Heinrichs & Zakzanis, 1998; Ranganathan & D'Souza, 2006a).

Although a number of studies have shown that THC consistently induces acute deficits in working memory, deficits are not consistent across different tasks. For instance, while THC has been shown to increase reaction time and disrupt performance on the Sternberg and N-back tasks (Bocker et al., 2010, Hunault et al., 2009; Ilan, Gevins, Coleman, ElSohly, & de Wit, 2004, 2005; Ilan, Smith, & Gevins, 2004), the effects on digit span and delayed match to

sample tasks have been mixed (Ballard & de Wit, 2011; D'Souza et al., 2004; D'Souza, Ranganathan, et al., 2008c; Morrison et al., 2009) and no effects have been detected on the serial sevens task (Curran, Brignell, Fletcher, Middleton, & Henry, 2002). Regarding verbal memory, THC has been shown to induce robust dose-dependent deficits in verbal learning and recall as measured by the Hopkins Verbal Learning Test (HVLT): THC disrupted both immediate and delayed (30 min) verbal recall (Fig. 4), and increased the number of "false positive" and "intrusion" responses (D'Souza et al., 2004, 2005; Morrison et al., 2009).

Finally, abnormalities in time perception that have been reported in schizophrenia (Carroll, O'Donnell, Shekhar, & Hetrick, 2009; Davalos, Kisley, & Ross, 2003; Tysk, 1983) are reproduced in healthy people under the acute effect of cannabinoids (Hicks, Gualtieri, Mayo, & Perez-Reyes, 1984; Mathew, Wilson, Turkington, & Coleman, 1998; McDonald, Schleifer, Richards, & de Wit, 2003a; Sewell et al., 2013b; Stone et al., 2010; Tinklenberg, Kopell, Melges, & Hollister, 1972). In the largest experimental study to date, Sewell et al. (2013a, 2013b) showed that different doses of THC acutely induce time overestimation and underproduction in healthy people (Sewell et al., 2013b). This is consistent with studies in nonhuman primates and rodents, which have also found that cannabinoids acutely induce deficits in time perception (Conrad, Elsmore, & Sodetz, 1972; Han & Robinson, 2001; McClure & McMillan, 1997; Schulze et al., 1988).

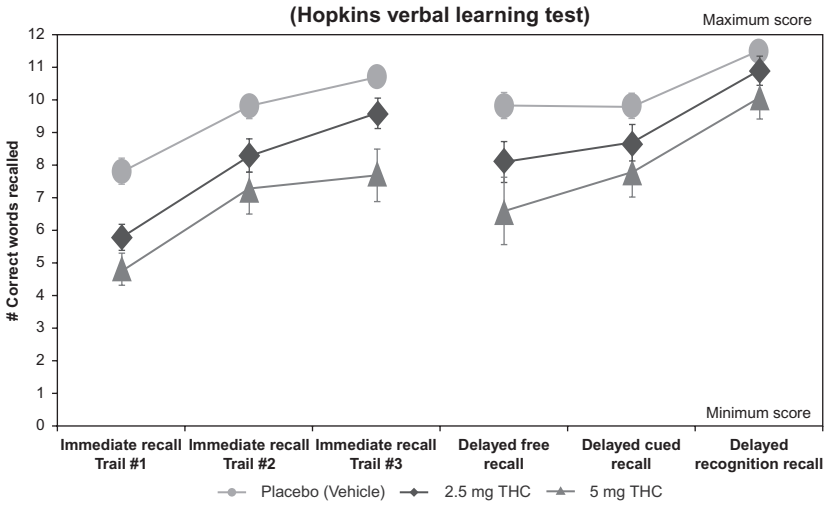

FIG. 4 Effects of THC on learning, immediate free recall, delayed free recall, delayed cued and recognition recall in healthy individuals, measured by a 12-word learning task (Hopkins Verbal Learning Test). *Reprinted with permission from D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. T., et al. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis.* Neuropsychopharmacology, 29*, 1558–1572.*

Effects in Individuals With Schizophrenia

Psychopharmacological challenge studies in clinical populations such as individuals with psychosis, cannabis use disorders, and a genetic risk for psychosis have been carried out using a variety of pharmacological stimuli including ketamine (Lahti, Koffel, LaPorte, & Tamminga, 1995), amphetamine (Laruelle et al., 1996), methylphenidate (Lieberman et al., 1984), and THC (D'Souza et al., 2005). Such studies have the potential to elucidate the complex involvement of individual neurotransmitter systems in the pathophysiology of various psychotic symptoms and substance use disorders and develop paradigms for testing treatments. However, perhaps due to theoretical safety and tolerability concerns, in addition to important ethical considerations, these studies are less numerous. Most of the HLS using cannabinoids in clinical populations are subsequently summarized in detail.

D'Souza 2005 (D'Souza et al., 2005): This was a 3-day, double-blind, randomized, placebo-controlled study, in which the behavioral and cognitive effects of 0 mg (placebo) and two active doses (2.5 and 5 mg IV THC) were characterized in 13 stable, antipsychotic-treated schizophrenia patients. Out of the 13 subjects, 10 were on typical antipsychotics (haloperidol and fluphenazine) and three were on atypical antipsychotics (risperidone and olanzapine). Behavioral outcomes included the PANSS and showed that THC transiently increased scores of the positive symptoms subscale (dose × time $F(4,68) = 4.90$, $P < 0.0016$) (Fig. 2). The positive symptoms induced by THC were not new symptoms, but symptoms previously endorsed by the subjects. On the negative subscale, THC transiently increased the scores with a significant effect of dose.

Overall this study showed that THC caused a transient increase in positive and negative symptoms, and worsened cognitive deficits in clinically stable patients with schizophrenia who were treated with antipsychotic drugs. Compared with matched controls, schizophrenia patients were more vulnerable to the psychosis-increasing and memory-impairing effects of THC. There were no serious short- or long-term adverse events associated with study participation, other than a case of exacerbation of hypertension that a subject failed to disclose at the time of screening. Furthermore, that THC did not reduce any of the core symptoms of schizophrenia raised questions about the commonly held view of a "self-medication" hypothesis of cannabis use and schizophrenia.

Henquet 2006 (Henquet et al., 2006a): Henquet et al. hypothesized that psychometric psychosis (measured by the Community Assessment of Psychotic Experiences or CAPE) and functional polymorphisms of the Catechol-O-Methyltransferase (COMT) gene (Val-Val/Val-Met/Met-Met) represented two different mechanisms impacting the same final common pathway of developing psychosis after cannabis exposure. To replicate and extend this finding, they conducted a double-blind, placebo-controlled crossover design in which patients with a psychotic disorder ($n = 30$), relatives of patients with a psychotic disorder ($n = 12$), and healthy controls ($n = 32$) were exposed to THC or placebo

cigarettes, followed by cognitive assessment and assessment of current psychotic experiences. In the 30 patients, lifetime diagnoses were: schizophrenia ($n=11$), schizoaffective disorder ($n=11$), and psychosis not otherwise specified ($n=8$). Twenty-two patients were using antipsychotic medication at the time of testing and eight were medication-free or used medication other than antipsychotic medication. Within the relatives group, three subjects had a lifetime diagnosis of bipolar disorder and one major depressive disorder. The COMT genotype distribution in the whole sample was 26% (Met/Met), 27% (Val/Val), and 47% (Val/Met).

On behavioral outcomes as measured by the PANSS, THC was not associated with a significant increase in positive symptoms, and no significant condition-by-genotype interaction was observed on the psychotic symptom outcome. However, there was a significant three-way condition-by-genotype-by-CAPE-trait interaction, which indicated that preexisting psychosis liability influenced the genetic moderation of THC-induced expression of psychosis. Thus, there was a significant condition-by-genotype interaction in the high CAPE-trait group.

On the Dutch visual verbal learning test, THC impaired verbal memory performance on immediate and delayed free recall as well as on delayed recognition. On the delayed recognition task, THC exposure caused significant impairment in subjects with the Val/Val genotype. The two-way condition-by-genotype interaction suggested that the effect in the Val/Val genotype was greater than that in the Val/Met and Met/Met genotypes.

In brief, Henquet et al. found that genetic predisposition and psychometric psychosis influenced the impact of THC on cognition and psychosis outcomes. They also concluded that the functional polymorphism of the COMT gene moderated sensitivity to the effects of THC on psychotic symptoms and that the differential sensitivity to THC associated with COMT genotype was in part conditional on additional evidence of psychosis liability (Val carriers with higher psychometric psychosis liability experienced more THC-induced transient psychotic symptoms compared with Val carriers without these additional measures of liability). This conditionality on additional psychometric psychosis liability was less evident for the cognitive measures.

Effects in Cannabis Users

Ramaekers 2009 (Ramaekers, Kauert, Theunissen, Toennes, & Moeller, 2009): This study tested whether heavy cannabis users developed tolerance to the cognition-impairing effects of THC. To test this, 24 subjects (12 occasional cannabis users and 12 heavy cannabis users) participated in a double-blind, placebo-controlled, two-way mixed model design. Both groups received single doses of placebo and 500 µg/kg THC by smoking. Performance tests included measures of perceptual motor control (critical tracking task), dual task processing (divided attention task), motor inhibition (stop signal task), and cognition (Tower of London). They found that THC-induced impairment of critical tracking

performance only occurred in occasional cannabis users when compared with heavy users as indicated by a significant THC-by-cannabis use history interaction ($P=0.027$). Performance in the divided attention task was significantly affected by THC, as indicated by increased tracking error ($P=0.013$) and the number of control losses ($P=0.032$) in the primary task and a decreased number of hits in the secondary task ($P=0.024$). Again, the overall effect of THC was more prominent in occasional cannabis users compared with heavy users. In the stop signal task, stop reaction time was affected by THC-by-time after smoking and there was no influence of a previous cannabis use history. Performance on the Tower of London task was not affected by THC. Overall, these data indicated that cannabis use history strongly determined the cognitive response to single doses of THC.

D'Souza et al. (2008a)*:* In this 3-day, double-blind, randomized, placebo-controlled study, the dose-related effects of 0, 2.5, and 5 mg IV THC were studied in 30 individuals who used cannabis about once weekly and were compared to 22 healthy controls. THC transiently increased (dose × time $P<0.0001$) clinician-rated perceptual alteration scores. Weekly users showed smaller THC-induced increases in the perceptual alterations scores (group × dose × time $P<0.001$), group × dose effect ($P<0.069$), and group effect ($P<0.006$). THC transiently increased psychosis (PANSS total scores) in both groups (dose × time $P<0.0001$), but weekly users had smaller increases compared with healthy controls (group × dose × time $P<0.0025$). THC also transiently increased VAS "high" scores in both groups (dose × time $P<0.0001$), but there was no group effect on this increase.

On cognitive measures, THC impaired immediate recall in both groups in a dose-related manner ($P<0.0001$) with a significant group-by-dose interaction ($P<0.03$), with weekly users performing worse at baseline (placebo condition), yet showing smaller THC-induced recall impairments than controls. THC impaired delayed recall in both groups with a significant group-by-dose interaction ($P<0.02$), with weekly users showing smaller THC-induced recall impairments than controls. On tasks of vigilance, THC increased omission and commission errors in both groups. While there was no group effect for both omission and commission errors, there was a significant group-by-dose interaction, such that the difference between 5 mg and placebo dose was significant in weekly users but not in controls. Overall, these data suggested that weekly users of cannabis are either inherently blunted and/or develop tolerance to their response to the psychotomimetic, perceptual altering, and amnestic effects of cannabinoids.

Kuepper et al. (2013a)*:* In this study, striatal dopamine release following smoked THC was measured using a single dynamic positron emission tomography (PET) scanning session in nine healthy cannabis users (average risk of psychotic disorder), eight patients with psychotic disorder (high risk of psychotic disorder), and seven unrelated first-degree relatives (intermediate risk of psychotic disorder). Compared with the control group, both patients and relatives showed significant displacement of the ligand (F18Fallypride) in striatal

subregions, indicative of dopamine release. This was most pronounced in the caudate nucleus. Behavioral measures including visual analog ratings of "feeling high," "internal perception," and "external perception" did not differ based on group (control, relatives, or patients).

Ranganathan et al. (2014): This study tested the effects of THC on individuals with a family history of alcoholism based on preclinical evidence suggesting that brain cannabinoid receptor function may mediate the effects of alcohol and risk for developing alcoholism. Thirty healthy subjects with varying degrees of family history of alcoholism were enrolled in this 3-day test study, during which they received 0.018 and 0.036 mg/kg of THC or placebo intravenously in a randomized, counterbalanced order under double-blind conditions. Greater degree of family history was correlated with greater "high" and perceptual alterations induced by THC, measured by a VAS and the CADSS, respectively. The interaction between THC dose and degree of family history on peak change in self-reported "high" was significant ($P = 0.03$). On the HVLT, THC significantly reduced total immediate free recall and long delayed free recall in a dose-dependent manner, but there was no effect of family history of alcoholism.

FACTORS MODULATING THE PSYCHOTOMIMETIC AND COGNITIVE EFFECTS OF Δ^9-TETRAHYDROCANNABINOL IN HLS

Gene-Drug Interactions

As mentioned above, cannabinoids have been shown to induce a number of transient schizophrenia-like effects in healthy people. The intensity of these effects varies across individuals with similar levels of exposure to cannabinoids. The effects can range from small perceptual alterations to transient episodes of frank paranoia or psychosis in a very small percentage of people. It is likely that some of these individual differences could be explained by genetic polymorphisms implicated in schizophrenia. In one of the first gene-by-environment studies, Caspi et al. demonstrated that a common polymorphism of the COMT gene, which encodes for an enzyme that plays an important role in the breakdown of dopamine in the prefrontal cortex (Papaleo et al., 2008), moderated the risk of schizophrenia in individuals exposed to cannabis (Caspi et al., 2005). The longstanding association between schizophrenia and alterations in the dopaminergic system (Howes & Kapur, 2009) has led others to explore the relationship between the acute response to cannabinoids and genes involved in the transmission or metabolism of brain dopamine.

A common variant of the COMT gene is the $Val^{158}Met$ polymorphism (rs4680), in which a G/A base-pair substitution results in an amino acid change from valine (Val) to methionine (Met) at codon 158 (Lachman et al., 1996). The rate of dopamine catabolism of the Val variant is up to 4 times the rate of the Met variant; thus, Val carriers have lower levels of extracellular dopamine

in the prefrontal cortex (Chen et al., 2004). It has been proposed that the Val variant confers an increased risk for schizophrenia in people exposed to cannabis during adolescence; however, a number of studies examining this issue have shown mixed results (Caspi et al., 2005; Kantrowitz et al., 2009; Pelayo-Teran et al., 2010; Zammit et al., 2007). In a study assessing the interaction between the COMT polymorphism and acute effects of cannabinoids, Henquet et al. (2006a, 2006b, 2006c) found that in individuals having both one copy of the Val allele and high scores on a measure of psychosis liability, THC induced greater schizophrenia-like effects (Henquet et al., 2006b). Furthermore, individuals with two copies of the Val allele had increased sensitivity to the acute effects of THC on cognition.

The **Dopamine Transporter 1** gene (**DAT1/SLC6A3**) encodes the dopamine transporter (DAT), a transmembrane transport protein that regulates the reuptake of dopamine from the synapse into the presynaptic terminal. In the striatum, the clearance of dopamine from the synapses is highly dependent on the DAT; thus, it has been argued that polymorphisms of the DAT1 gene may be involved in the high levels of striatal dopaminergic activity observed in some patients with schizophrenia. Concordantly, a polymorphism of the DAT1 gene associated with higher striatal dopamine has been linked to schizophrenia (Talkowski et al., 2008).

The **AKT1** gene encodes the **protein kinase B**, an integral component of the dopamine signaling cascade (Beaulieu, Gainetdinov, & Caron, 2007) that has been associated with schizophrenia (Emamian, Hall, Birnbaum, Karayiorgou, & Gogos, 2004; Thiselton et al., 2008). Regarding the association between DAT1 variations and the acute effect of cannabinoids, Bhattacharyya et al. showed that carriers of the 9-repeat allele of the DAT1 gene which were also G homozygotes of the rs1130233 SNP of the AKT1 gene had increased schizophrenia-like symptoms in response to THC (Bhattacharyya, Atakan, et al., 2012b). Cannabinoids activate the AKT1 pathway via CB_1 and CB_2 receptors, representing a potential mechanism for psychosis. However, Bhattacharya et al. found that the GG genotype (a single nucleotide polymorphism) of the AKT1 gene reduced sensitivity to the acute psychosis-inducing effects of THC. More recent large epidemiological studies have further implicated other polymorphisms of this gene in increased susceptibility for THC-induced psychosis, supporting the HLS.

Other genetic variation in AKT1 has been hypothesized to increase sensitivity to the psychotomimetic effects of cannabis as well as confer increased risk for cannabis-associated psychotic disorders. This has been supported by case–control studies showing that a polymorphism of the AKT1 rs2494732 locus (C/C versus T/T) interacts with cannabis use to infer a greater likelihood of later developing a psychotic disorder (Di Forti et al., 2012) as well as worse performance in a continuous performance task in individuals with psychosis (van Winkel, van Beveren, Simons, & Genetic Risk and Outcome of Psychosis (GROUP) Investigators, 2011). Recently, using a hybrid naturalistic challenge

study design, Morgan, Freeman, Powell, and Curran (2016) studied the acute response to smoked cannabis in 442 healthy young cannabis users while intoxicated with their own cannabis. They found that variation at the rs2494732 locus of the AKT1 gene predicted acute psychotomimetic response (as measured by total score on the PSI, (Mason, Morgan, Stefanovic, & Curran, 2008)), dependence on the drug, and baseline schizotypy (Morgan et al., 2016). Another study indicates that a variant in the D2 receptor gene may also increase psychosis risk, and that the risk may be greater in carriers of both this variant and the AKT1 risk allele (Colizzi et al., 2015).

Interactions With Other Drugs

A further significant finding of HLS using THC is the dissociation between serum levels and peak clinical effects. Even following IV administration, subjective effects can be delayed by 15 min. This might suggest that the psychotomimetic effects of THC are downstream to its primary site of action—the CB_1 receptor. The ubiquitous nature and known neuromodulatory role of the endocannabinoid system suggests that THC induces its psychotomimetic effects via interactions with other neurotransmitter systems with more established links to schizophrenia.

Preclinical studies demonstrate that THC administration increases striatal dopamine, but human data are mixed. D2 receptor blockade (via single doses of olanzapine or haloperidol) attenuated the acute psychotomimetic effects of THC in healthy subjects in two (Kleinloog et al., 2012a) of the three HLS using this paradigm (D'Souza, Braley, et al., 2008). In individuals with schizophrenia, long-term antipsychotic use failed to protect them from the acute psychosis-exacerbating effects of THC (D'Souza et al., 2005). Results of preclinical and human studies exploring the ability of THC to increase striatal dopamine (Barkus et al., 2011; Bossong et al., 2009; Kuepper et al., 2013b; Stokes, Mehta, Curran, Breen, & Grasby, 2009), as well as direct interactions between CB_1 and D2 receptors (Glass & Felder, 1997; Munoz-Arenas et al., 2015), are similarly mixed. Pooling of two cohorts, in order to achieve higher power, a small but significant displacement of [^{11}C]raclopride was observed in the ventral striatum after THC administration (Bossong et al., 2009), indicating increased endogenous dopamine activity at D2 receptors, but whether this small change can explain the psychotomimetic effects of THC is not clear.

Confirming a wealth of preclinical data indicating extensive interactions between the endocannabinoid and GABAergic systems, Radhakrishnan et al. showed that a pharmacologically induced GABA deficit (produced by Iomazenil—a GABA-A negative allosteric modulator) enhanced THC-induced psychotomimetic effects in healthy humans (Radhakrishnan et al., 2015). Particularly prevalent in the cortex and hippocampus, the activation of CB_1 receptors inhibits the release of GABA by cholecystokinin basket cells, leading to disruption of the cortical inhibitory/excitatory balance (Farkas et al., 2010).

This mechanism may have particular relevance to the connection between cannabis and schizophrenia (Sherif et al., 2016).

As the second most pharmacologically significant cannabinoid in cannabis, CBD has garnered increasing attention in both the scientific literature and popular press. Although its effects on the endocannabinoid system have not been fully elucidated, contrary to THC, it exhibits CB_1 receptor antagonism/inverse agonism and fatty acid amide hydrolase (FAAH) inhibition. This pattern of effects, alongside limited clinical evidence, has identified CBD as the potential natural modulator of effects of THC in cannabis (Leweke, 2007), prompting several HLS. Pretreatment with CBD has been shown to attenuate THC-induced psychotomimetic effects, paranoia, and verbal memory impairment (Bhattacharyya et al., 2015; Englund et al., 2013b; Ilan et al., 2005; Leweke et al., 2000; Martin-Santos et al., 2012b). Head to head, THC produced increased psychotic symptoms and skin conductance responses during processing of fearful faces, whereas CBD produced a reduction in anxiety and decreased skin conductance (Fusar-Poli et al., 2009). Second, during functional magnetic resonance imaging (fMRI) tasks testing verbal recall, response inhibition, processing fearful faces, and auditory and visual processing, THC and CBD had divergent effects on blood-oxygen-level dependent (BOLD) response (Bhattacharyya et al., 2010; Borgwardt et al., 2008; Fusar-Poli et al., 2009).

PSYCHOPHYSIOLOGICAL MARKERS OF PSYCHOTOMIMETIC AND COGNITIVE EFFECTS OF Δ^9-TETRAHYDROCANNABINOL IN HUMAN LABORATORY STUDIES

Typical techniques of measuring the psychotomimetic and cognitive effects of THC in HLS involve rating scales and hence are limited by subjectivity on both the part of the participant and the rater. Biomarkers—neural correlates of these clinical effects—may provide a complementary set of objective measures. In HLS, the neural effects of cannabinoids have been primarily studied using electroencephalography (EEG), which is one of the only noninvasive techniques capable of capturing neural activity in real time. In general terms, at the cellular level, neural activity consists of controlled exchanges of ions between the intra- and extracellular spaces of neurons. These exchanges cause fluctuations in the extracellular electric potential fields, that, when summed together across large populations (hundreds of millions) of similarly oriented groups of neurons (particularly pyramidal cells) (Niedermeyer & da Silva, 2005), produce electric potential fluctuations that can be measured at the scalp with an EEG. The strength of the resulting signals would depend on both the number of active pyramidal cells and the level of synchronization of the active neurons, given that desynchronized neurons would tend to cancel out by destructive interference their individual contributions to the summed electric potential (Lachaux, Axmacher, Mormann, Halgren, & Crone, 2012).

Brain functions such as attention, working memory, emotions, and language, rely on the integrity of both short-scale (within areas) and long-scale (between areas) neural networks (Bullmore & Sporns, 2009; Varela, Lachaux, Rodriguez, & Martinerie, 2001). By engaging their nodes in synchronous patterns of oscillatory electrical activity, neural networks integrate and process information (Singer, 1999). Thus, deficits affecting the generation of neural oscillations, the signal-to-noise ratio of the circuit, or the communication between nodes such as the ones observed in schizophrenia and under the acute effect of cannabinoids (Cortes-Briones, Cahill, et al., 2015b; Diez, Suazo, Casado, Martin-Loeches, & Molina, 2013; Díez et al., 2014; Higashima et al., 2007; Hinkley et al., 2011; Kubicki et al., 2003, 2005; Lawrie et al., 2002; Seok et al., 2007; Uhlhaas, Haenschel, Nikolić, & Singer, 2008; Whitfield-Gabrieli et al., 2009, Winterer & Weinberger, 2003; Winterer et al., 2000, 2004; Yang et al., 2014), likely underlie some of the disruptions in brain function (e.g., abnormal perceptual experiences) observed in both cases.

It has been proposed that CB_1 receptors located on the axon terminals of cholecystokinin (CCK)-expressing GABAergic interneurons in the cerebral cortex and hippocampus are part of a noise filter-like mechanism that enhances the signal-to-noise ratio of neural networks (Bartos & Elgueta, 2012; Csicsvari, Jamieson, Wise, & Buzsáki, 2003; Tukker, Fuentealba, Hartwich, Somogyi, & Klausberger, 2007). This mechanism relies on the physiologic, space-localized, on demand, brief activation of CB_1 receptors by endocannabinoids released by active pyramidal cells. Thus, the nonphysiologic, global, long-lasting activation of CB_1 receptors by exogenous cannabinoids such as THC could disrupt the CB_1 receptor-mediated noise filter mechanism, reducing the signal-to-noise ratio of the system. This transient change in the dynamics of neural networks induced by exogenous cannabinoids has been proposed to mimic some important aspects of the long-lasting abnormalities in the dynamics of neural networks present in schizophrenia (Cortes-Briones, Skosnik, et al., 2015; Cortes-Briones, Cahill, et al., 2015b).

Event-Related Potentials

Event-related potentials (ERPs) are transient changes in the electric potential (voltages) recorded at the scalp with EEG in response and time-locked to the presentation of stimuli. Numerous ERPs have been studied, with each thought to correspond to varying aspects of neural processing (e.g., early sensory processing, attention, and language processing) (Luck & Kappenman, 2012). Depending on the specific kind of stimuli used to elicit them, ERPs have either a positive (denoted with a "P") or a negative (denoted with an "N") polarity that peaks at a specific poststimulus latency (e.g., 300 ms). This is reflected on the names of ERPs (e.g., N100 indicates a negative response peaking 100 ms after the onset of the stimuli).

The ***P300*** is a positive voltage response peaking around 300 ms after stimulus presentation, elicited by novel (P3a) and target deviant (P3b) stimuli (visual

or auditory) presented with a low probability (~10%–20% of all stimuli) within a sequence of repetitive, highly probable stimuli (~80%–90% of all stimuli). P300 is thought to be related to directed attention, contextual updating of working memory, and the attribution of salience to novel and deviant stimuli (Polich & Criado, 2006). P300, particularly the P3b component, is thought to result from the activity of a distributed neural network including the thalamus, hippocampus, inferior parietal lobe, superior temporal gyrus, and frontal cortex (Kiehl, Laurens, Duty, Forster, & Liddle, 2001). Deficits in P300 amplitude and latency have been demonstrated in patients with schizophrenia (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004; Bramon et al., 2005; Jeon & Polich, 2003; Solowij & Michie, 2007; Turetsky et al., 2007). Interestingly, studies have shown that both oral and smoked THC acutely reduces P300 amplitude (Ilan et al., 2005; Roser et al., 2008). P300 amplitude reductions have even been observed in heavy cannabis users after smoking THC, indicating that the acute deficits in P300 amplitude induced by THC may be resistant to the effects of tolerance (Theunissen et al., 2012). In a double-blind, placebo-controlled, counterbalanced, and crossover study using IV administration of THC, D'Souza et al. (2012a, 2012b) demonstrated that both P3a and P3b amplitudes were disrupted by THC in a dose-dependent manner (D'Souza et al., 2012b). These deficits were not observed during early sensory-related ERPs (N100), suggesting that THC-induced deficits are greater in late processes involving novelty, saliency, and working memory context updating. Furthermore, the reductions in P3b amplitude were correlated with the psychotomimetic effects of THC.

Mismatch negativity (MMN) is a negative voltage response peaking around 100–200 ms after stimulus presentation, elicited by auditory stimuli that deviate in frequency or duration from a sequence of standard auditory stimuli. It is thought to be an index of basic auditory processing and sensory memory that is relatively independent of attention. Its neural sources have been localized in the superior temporal and prefrontal cortex (Naatanen & Alho, 1995; Rinne, Alho, Ilmoniemi, Virtanen, & Naatanen, 2000), which is consistent with an index of early auditory processing. Regarding the acute effect of cannabinoids on MMN, Juckel, Roser, Nadulski, Stadelmann, and Gallinat (2007) examined the effects of oral THC and THC plus CBD. They found that oral THC had no effect on MMN amplitude compared to placebo (Juckel et al., 2007). Interestingly, THC + CBD was found to increase the amplitude of the MMN, which the authors interpreted as a result of the antipsychotic effects of CBD. The lack of effect on MMN amplitude with THC alone could be related to the low dose of THC chosen (10 mg orally), or due to the inter- and intraindividual variability associated with oral routes of administration.

Neural Oscillations: Steady-State Response

Reduced gamma-band (~40 Hz) auditory steady-state response (ASSR) has been observed in first episode and chronic schizophrenia (Krishnan et al.,

2009; Kwon et al., 1999; Light et al., 2006; Spencer, Salisbury, Shenton, & McCarley, 2008a). Furthermore, this deficit has been associated with some characteristic abnormalities of the disorder (e.g., positive symptoms and working memory deficits) (Light et al., 2006; Spencer, Salisbury, Shenton, & McCarley, 2008b). Cortical θ and γ oscillations are dependent on perisomatic inhibition of pyramidal neurons from basket cells expressing cholecystokinin (CCK(b) cells) and parvalbumin [PV(b) cells], respectively. Alterations in basket cells may underlie the cortical oscillation deficits in schizophrenia. CB_1 receptors are located at the terminals of CCK-containing GABAergic interneurons. In preclinical studies, cannabinoids have been shown to reduce γ oscillations in hippocampal slice preparations. Despite these findings, so far there has been only one study examining the acute effects of cannabinoids on the ASSR and the relationship between these effects and the psychotomimetic effects of THC. In a double-blind, randomized, crossover, and counterbalanced study in which subjects received IV THC (placebo, 0.015 and 0.03 mg/kg), Cortes-Briones, Skosnik, et al. (2015), Cortes-Briones, Cahill, et al. (2015a), and Cortes-Briones, Cahill, et al. (2015b) showed, for the first time in humans, that THC acutely disrupts gamma-band (40 Hz) oscillations using an ASSR paradigm (Cortes-Briones, Skosnik, et al., 2015). Specifically, this study showed a dose-dependent reduction of intertrial coherence (ITC) (a measure of the consistency of the brain's response across trials) for 40 Hz stimulation. Furthermore, the authors showed that the higher dose of THC (0.03 mg/kg) reduced evoked power during 40 Hz stimulation at a trend level, and that the effects of THC on ITC and evoked power were reduced in subjects with a recent use of cannabis. No significant effects were found for the 20 or 30 Hz ASSRs, suggesting a selective effect of cannabinoids on evoked gamma-band activity. Interestingly, an inverse relationship between ITC and the schizophrenia-like effects of THC was found, suggesting that some of the psychotomimetic effects of cannabinoids may be related to their capacity to disrupt gamma-band oscillations. Considering that ITC measures reflect the consistency (nonrandomness) of the brain's response to different occurrences (trials) of a stimulus/event, the authors hypothesized that these findings suggest that the schizophrenia-like effects of THC may be related to an increased variability (randomness) in the brain's response to stimulation.

Neural Noise

There is growing evidence supporting the idea that neural noise, that is, the randomness of neural activity, is increased in patients with schizophrenia (Diez et al., 2013; Díez et al., 2014; Winterer & Weinberger, 2003, Winterer et al., 2000, 2004). Several studies have shown increased trial-to-trial (random) variability of evoked EEG responses in schizophrenia (Diez et al., 2013; Díez et al., 2014; Ford, White, Lim, & Pfefferbaum, 1994,

Winterer et al., 2000, 2004). Furthermore, nonlinear measures of uncertainty (entropy) or randomness have shown increased *randomness* in the EEG and Magnetoencephalography (MEG) signals of patients with schizophrenia (Li et al., 2008; Takahashi et al., 2010; Fernández, Gómez, Hornero, & López-Ibor, 2013), which are higher during periods of psychotic decompensation (Takahashi et al., 2010).

So far, only one study has investigated the effect of cannabinoids on neural noise in humans, and the relationship between this effect and behavior. In a recent study, Cortes-Briones et al. used Lempel-Ziv complexity (LZC), a measure from information theory first developed to characterize the randomness of signals, to test the hypothesis that THC increases neural noise (Cortes-Briones, Cahill, et al., 2015a). Furthermore, they tested the hypothesis that there is a positive relationship between neural noise and the schizophrenia-like effects of THC that is independent of the effect of THC on signal power. Using a double-blind, randomized, crossover, and counterbalanced design in which subjects received IV THC (placebo, 0.015 and 0.03 mg/kg), the authors measured LZC in the baseline period of an oddball task. The results showed that THC increased neural noise in a dose dependent manner, and that there was a strong positive relationship between neural noise and the psychosis-like positive ($\beta = 0.685$) and disorganization ($\beta = 0.754$) symptoms induced by THC. Interestingly, no relationship between neural noise and negative-like symptoms was found. Importantly, these relationships were independent of the changes in signal power induced by THC. Considering the idea that random noise can interfere with and distort the information circulating between the nodes of a network, the authors hypothesized that by increasing neural noise THC may be inducing a *dysconnectivity* (aberrant connections) (Stephan, Friston, & Frith, 2009) between the nodes of the brain's networks, and that this effect could be responsible for some of the psychotomimetic effects of THC.

Neuroreceptor Imaging

In addition to EEG, other neuroimaging modalities have been utilized to identify more proximate markers of the neural changes resulting from THC administration and, in some instances, correlated with the psychotomimetic and cognitive effects (summarized in Table 2).

The results of neuroreceptor imaging to study the ability of THC to increase striatal dopamine (Barkus et al., 2011; Bossong et al., 2009; Kuepper et al., 2013b; Stokes et al., 2009) are mixed. Although there is some evidence of displacement of [^{11}C]raclopride in the ventral striatum following THC administration, the relationship with psychotomimetic effects has not been well established.

Kuepper et al. studied striatal dopamine release following vaporized THC (8 mg) and placebo and showed that compared with healthy controls,

both patients and relatives of those with psychosis showed significant displacement of the ligand ([F-18]fallypride) in striatal subregions, indicative of dopamine release with the biggest effect in the caudate nucleus (Kuepper et al., 2013a).

Functional Imaging

In a large study of cannabis users using PET and O^{15} H_2O, Mathew et al. demonstrated an association between decreased cerebellar blood flow and THC-induced timing deficits (Mathew et al., 1998). The effects of THC have also been studied using fMRI. THC and CBD appear to have opposing effects on BOLD signal (Bhattacharyya et al., 2010; Winton-Brown et al., 2011). Notably, a few studies show correlations between psychotomimetic (but not yet cognitive) effects and perturbation in BOLD signal. Bhattacharya et al. reported an increased BOLD activation in the parahippocampal gyrus and attenuation in the ventral striatum, correlated with psychotomimetic symptoms (Bhattacharyya et al., 2009). In a further study, attenuated task-related activation of the right caudate was inversely correlated with severity of symptoms. In a preliminary study, Bhattacharyya et al. have also suggested that, in individuals with specific polymorphisms of both the ATK1 and DAT1 genes, THC-induced psychotomimetic effects could be mediated by attenuation of activity in the striatum and midbrain (Bhattacharyya, Atakan, et al., 2012b).

As discussed earlier, cannabinoids produce robust impairments of learning and memory. Bhattacharyya et al. reported that oral THC (10 mg) altered medial temporal activation during the encoding phase of a verbal paired associate learning task in healthy males ($n = 15$) (Bhattacharyya et al., 2009). THC also attenuated striatal activation during recall that was correlated with the positive symptoms of psychosis.

The effects of oral THC on response inhibition have been studied using a go/no-go task (Bhattacharyya et al., 2015; Borgwardt et al., 2008). THC attenuated activation in the inferior frontal, anterior cingulate, and precuneal cortices, and augmented activation in the medial temporal cortex and caudate. Bhattacharrya et al. further reported that the effect of THC on inferior frontal activation correlated with the severity of the positive psychotic symptoms. Of note, patients with psychosis show altered striatal and prefrontal activation during inhibition tasks (Kaladjian et al., 2007; Rubia et al., 2001).

THC has also been reported to attenuate amygdalal, hippocampal, parietal, and prefrontal activation to fearful faces, and augment activation of these regions to happy faces (Bossong et al., 2013). THC has also been reported to reduce the amygdalal response to threat-related faces (Phan et al., 2008) and may increase functional connectivity between frontal regions and amygdalal subnuclei (Gorka et al., 2015).

CONCLUSIONS

HLS using THC have reliably demonstrated an array of dose-dependent psychotomimetic and cognitive effects in healthy humans, as well as in individuals with cannabis use disorder, increased risk of psychosis, and schizophrenia. Broadly, deficits are observed in domains most relevant to schizophrenia: positive, negative, dissociative, and disorganization cluster symptoms and impairment in working and verbal memory. Laboratory models of psychosis may enrich our understanding of psychotic disorders such as schizophrenia, offering methodological advantages. The ability to extrapolate the results of HLS in healthy THC users to clinical psychosis is supported by the fact that these effects are intensified in individuals who are diagnosed with or at risk for schizophrenia. A range of more proximate markers of neuronal function have been discovered, some highly associated with clinical effects. Genetic variations and the presence of other drugs may modulate the effects.

HLS have demonstrated value in the immediate study of acute, intoxication-related, cannabis-induced psychosis, in addition to providing insights into mechanisms underlying the shared phenomenology observed with schizophrenia. Already, for example, HLS comparing the interactive effects of THC and CBD have lent support for completed and ongoing clinical trials of the latter for schizophrenia. Furthermore, novel biomarkers of psychosis, designed and refined within laboratory settings, are being tested in clinical populations with great potential relevance for screening, prediction of relapse, and monitoring of treatment response. A further novel use of laboratory-based cannabinoid challenges as a neuropsychiatric "stress test" has been proposed (Gupta, Ranganathan, & D'Souza, 2016a). As a screening test, akin to cardiac stress testing for coronary ischemia, THC may be administered within safe, controlled parameters to those suspected to be at risk of schizophrenia in order to ascertain clinical or subclinical (e.g., electrophysiological) changes, further quantifying risk and informing the utility of new or established interventions for primary or secondary prevention.

HLS provide a vital complement to other study designs within the field by allowing for more controlled confirmation and elucidation of mechanisms and more direct inference of causality. The ecological relevance of the numerous HLS using oral THC is increasing as "edibles" grow in popularity. Responding to changing content of the cannabis available in society, HLS may need to further explore higher doses of THC and the interactive effects of CBD. Similarly, HLS utilizing vaporized THC may become more prevalent. Capitalizing on established genetic, electrophysiological, biochemical, and neuroimaging-based correlates of psychosis, multimodal HLS in healthy cannabis users (perhaps in concert with other psychotomimetic drugs and individuals with schizophrenia) may further illuminate the degree of overlap between laboratory models and clinical psychotic states. The cross pollination resulting from the continued closure of the gap between the laboratory and the clinic can only serve to propel the field forward.

Key Chapter Points

- HLS using THC have reliably demonstrated a range of transient, dose-dependent psychotomimetic and deleterious cognitive effects in healthy individuals, as well as in those with cannabis use disorder, increased risk of psychosis, and schizophrenia.
- This type of study design complements more naturalistic or observational approaches by allowing for more controlled confirmation and elucidation of mechanisms as well as more direct inference of causality.
- Psychophysiological correlates of THC-induced psychosis-like states have been characterized, most notably in the EEG. These may have wider clinical potential as biomarkers of psychosis.
- Genetic variations (in COMT, DAT1, and ATK1 genes) and the presence of other drugs (such as haloperidol, iomazenil, and CBD) may modulate the effects.
- Future priorities for HLS include the further exploration of higher doses of THC, vaporized THC, and the interactive effects of CBD.

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WORK 3

Archival Report

The Psychosis-like Effects of Δ^9-Tetrahydrocannabinol Are Associated With Increased Cortical Noise in Healthy Humans

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ABSTRACT

BACKGROUND: Drugs that induce psychosis may do so by increasing the level of task-irrelevant random neural activity or neural noise. Increased levels of neural noise have been demonstrated in psychotic disorders. We tested the hypothesis that neural noise could also be involved in the psychotomimetic effects of delta-9-tetrahydrocannabinol (Δ^9-THC), the principal active constituent of cannabis.

METHODS: Neural noise was indexed by measuring the level of randomness in the electroencephalogram during the prestimulus baseline period of an oddball task using Lempel-Ziv complexity, a nonlinear measure of signal randomness. The acute, dose-related effects of Δ^9-THC on Lempel-Ziv complexity and signal power were studied in humans ($n = 24$) who completed 3 test days during which they received intravenous Δ^9-THC (placebo, .015 and .03 mg/kg) in a double-blind, randomized, crossover, and counterbalanced design.

RESULTS: Δ^9-THC increased neural noise in a dose-related manner. Furthermore, there was a strong positive relationship between neural noise and the psychosis-like positive and disorganization symptoms induced by Δ^9-THC, which was independent of total signal power. Instead, there was no relationship between noise and negative-like symptoms. In addition, Δ^9-THC reduced total signal power during both active drug conditions compared with placebo, but no relationship was detected between signal power and psychosis-like symptoms.

CONCLUSIONS: At doses that produced psychosis-like effects, Δ^9-THC increased neural noise in humans in a dose-dependent manner. Furthermore, increases in neural noise were related with increases in Δ^9-THC-induced psychosis-like symptoms but not negative-like symptoms. These findings suggest that increases in neural noise may contribute to the psychotomimetic effects of Δ^9-THC.

Keywords: Cannabinoids, Electroencephalogram, Neural noise, Nonlinear analysis, Psychosis, Tetrahydrocannabinol

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Complex mental processes such as perception, language, emotion, and memory rely on the integrity of long-range functional networks formed by ensembles of brain areas (nodes) processing information in a coordinated manner (1,2). Alterations in these networks and their information processing capabilities may contribute to the emergence of some core symptoms of psychosis such as hallucinations, delusions, and thought disorganization. Consistent with this view, converging lines of evidence from structural (diffusion tensor imaging) and functional (functional magnetic resonance imaging [fMRI], electroencephalogram [EEG], and magneto-encephalogram [MEG]) studies have shown abnormal neural connectivity in schizophrenia, which has been related to the presence and intensity of psychotic symptoms (3–9).

Concepts used to characterize the functioning of real-world complex networks (e.g., the internet) may provide valuable insights into the abnormalities underlying some psychotic symptoms. A network can be characterized as a set of interconnected nodes that exchange and process information in a coordinated manner. Information is transmitted from one node to another through a medium (e.g., a cable) as part of a signal (e.g., an electromagnetic wave), which is composed by information and random noise. The latter is a sum of random activity and interference caused by other signals travelling through the same medium. According to information theory, the upper limit of the total amount of undistorted (error-free) information per unit of time that can be carried by a signal is limited by: 1) the bandwidth (in Hz), 2) the total power, and 3) the amount of random activity or noise of the signal (10–13). Thus, keeping the bandwidth and the total power of a signal constant, the higher the level of noise, the lower the amount of information that can be carried by the signal without distortion. Increased noise may, therefore, disrupt the coordinated activity between nodes, resulting in the disruption of information processing.

There is growing evidence from EEG, MEG, and neuro-imaging studies suggesting increased randomness/noise in

the brain activity of schizophrenia patients (14–19). A number of studies have shown increased intertrial (random) variability in the latency and amplitude of evoked responses measured in the EEG of schizophrenia patients (14,16–18,20). Furthermore, measures developed to characterize the uncertainty (entropy) or randomness of signals have revealed increased levels of randomness in the EEG and MEG of schizophrenia patients (21–23), which are higher during periods of exacerbation of psychosis (22). While there may be limitations to the existing EEG and MEG literature, recent fMRI data provide further support to the hypothesis that noise is increased in schizophrenia (19).

A number of drugs, including ketamine, delta-9-tetrahydrocannabinol (Δ^9-THC), psilocybin, and amphetamine, have been used in the laboratory to study psychotic states and to understand the contributions of neurotransmitter systems to the pathophysiology of psychosis. The acute administration of Δ^9-THC, the primary psychoactive constituent in cannabis, and other agonists of brain cannabinoid receptors (type 1 cannabinoid receptor [CB1R]) have been shown to induce transient psychosis-like effects and psychophysiological abnormalities in healthy control subjects that share some similarities to those observed in schizophrenia [reviewed in (24–26)]. Furthermore, Δ^9-THC has been shown to increase psychotic symptoms transiently in stable schizophrenia patients (27). Studies in rats have shown that CB1R agonists acutely reduce the spectral power of local field potential (LFP) oscillations in a number of frequency bands within the hippocampus and entorhinal cortex (28,29). Importantly, this effect was not a consequence of a reduction in the individual neurons' activity but was related to an increase in the randomness/noise (decrease in the synchronization) of the neurons' activity (28,29). Considering that, as mentioned above, neural noise may be involved in the pathophysiology and phenomenology of schizophrenia, these findings raise the intriguing possibility that neural noise could also be involved in the acute psychotomimetic effects of Δ^9-THC and other CB1R agonists. To our knowledge, no studies in humans have tested this hypothesis.

Lempel-Ziv complexity (LZC) is a nonlinear measure first developed to characterize the level of randomness (30) or noise of signals. It is a measure of the minimum number of different terms (e.g., words) necessary to fully reconstruct a signal (e.g., sentence) without losing information. Applying this to EEG, LZC measures the minimum number of distinct patterns of activity that are necessary to characterize the behavior of a signal (Figure S1 in Supplement 1). The higher the randomness of a signal (e.g., the volume of the background babble of a crowded room), the larger is the minimum number of different terms (word fragments) necessary to reconstruct the signal and hence, the higher is LZC. For infinite random signals, which lack regular recurrent terms (e.g., white noise), the normalized value of LZC approaches 1, while for infinite regular (periodic) signals, it approaches 0 (31,32). LZC has been increasingly theoretically and empirically validated in the study of electrophysiological signals [reviewed in (21,33–38)].

Traditional measures of neural noise used to study the EEG and MEG of schizophrenia patients (14–18,39) have characterized noise as brain responses that are not time-locked to the stimuli in the context of time-locked paradigms (e.g., event-related potential). In this sense, neural noise refers to the random variation of the brain's response across the different trials of a task (i.e., intertrial variability). Thus, this conceptualization of noise provides information about the capacity of the brain to produce consistent patterns of activity in response to repeated presentations of a stimulus. In contrast to these measures, LZC provides direct information about the level of randomness of EEG signals (30), which makes it especially suited for detecting cannabinoid-induced changes in the randomness (noise) of the brain's electrical activity (28,29).

Until recently, brain activity during the baseline or prestimulation period received little attention. However, evidence from both animals and humans suggests that this period plays a key role in the brain's response to tasks. The characteristics (e.g., phase, randomness) of prestimulation brain activity are known to modulate the electrical and behavioral responses to tasks (40,41). More importantly, evidence for an interaction between aberrant (increased) baseline brain activity and a reduction of task-related poststimulus activity measured by both EEG (14) and fMRI (42) has been observed in schizophrenia patients. Furthermore, schizophrenia patients show increased baseline activity, especially in the gamma band, and an inverse relationship between prestimulation and poststimulation gamma activity (43). These findings suggest that at least part of the task-related abnormalities observed in schizophrenia may be associated with the presence of aberrant brain activity during the prestimulation period.

This study was part of a larger project that aimed to assess the dose-related effects of Δ^9-THC on several electrophysiological indices of information processing relevant to schizophrenia [e.g., P300 (44), oscillations, and neural noise] and to determine the relationship between the electrophysiological and behavioral effects of Δ^9-THC. Δ^9-THC was hypothesized to increase neural noise (LZC) during the prestimulation period of an oddball task and psychosis-like effects. Furthermore, we hypothesized that there would be a positive relationship between neural noise and the psychosis-like effects induced by Δ^9-THC and that this relationship would be independent of changes in signal power.

METHODS AND MATERIALS

A complete description of subjects, regulatory approvals, and general study procedures is included in Supplement 1 (see text and Table S1 in Supplement 1). In brief, in this 3 test day, randomized, double-blind, placebo-controlled, crossover study, subjects received Δ^9-THC (vehicle [ethanol], .015 mg/kg or .03 mg/kg) over 10 minutes by intravenous route. The sample included subjects with and without recent cannabis exposure (within the last 30 days) and excluded cannabis-naïve and cannabis-dependent subjects.

EEG Paradigm and Data Acquisition

A detailed account of the EEG paradigm and data acquisition procedure is provided in Supplement 1. Briefly, 22-electrode EEG data were recorded (sampling rate 1000 Hz) while subjects performed an auditory oddball task described elsewhere (44).

General EEG Preprocessing

A detailed description of the EEG preprocessing is provided in Supplement 1. Briefly, EEG data were bandpass filtered (.5–100 Hz; bandwidth = 99.5 Hz), and power line, muscle, eye movement, and blink artifacts were removed using multitapering (45), blind source separation (46), and adaptive filtering techniques (47), respectively. The data were segmented in 1150-ms epochs time-locked to stimulus onset with a 250-ms prestimulus segment. To minimize the confounding effect that muscle activity could have on measuring neural noise, only midline electrodes were used for statistical analyses, given that they tend to be less contaminated by muscle activity than the rest (48).

EEG Measures

Lempel-Ziv Complexity. A detailed description of the calculation of LZC is provided in Supplement 1. For each subject and electrode, LZC was calculated on the prestimulation segment (−250 to −1 msec) of each trial and then averaged across trials. Finally, a single LZC value was calculated for each subject by averaging LZC across electrodes.

Signal Power. For each subject, the signal power of each electrode was obtained by calculating the root-mean-square power (average of the squared amplitudes) of each trial's prestimulation interval (−250 to −1 msec) and then averaging across trials. Finally, for each subject, a single signal power measure was obtained by averaging across electrodes.

Behavioral Measures

The positive, disorganization, and negative symptom subscales from a five-factor model of the Positive and Negative Syndrome Scale (PANSS) (49) were used to measure psychosis-like and negative-like symptoms. This model was selected for its stability and for not excluding items from the final solution (50). By characterizing positive and disorganization symptoms, this five-factor model was hypothesized to more completely capture the range of psychosis-like effects induced by Δ^9-THC than the usual three-factor model of the PANSS.

Statistical Analysis

Data were examined descriptively using means, standard deviations, and distribution plots. In addition, each outcome was assessed for normality using the Kolmogorov-Smirnov test in each drug condition separately. Unless specified, statistical analyses were conducted using SPSS 21 (IBM Corporation, Armonk, New York).

Effect of Drug Condition on EEG Measures. The effect of drug condition (placebo, .015 mg/kg, and .03 mg/kg) on EEG measures was assessed using generalized estimating equations (GEEs) (51,52) with an unstructured working correlation matrix. GEE modeling is a robust method that corrects for correlated samples, handles missing data, and has been shown to be more powerful than typical repeated measures analysis of variance for small/medium-size samples (51–53). Independent GEE models were fitted for LZC with and without signal power as a covariate and p values were adjusted for two comparisons with the Holm-Bonferroni (HB) method. Pairwise comparisons (three per model) were conducted and p values were HB-adjusted for six comparisons. In addition, independent GEE models were fitted for signal power with and without LZC as a covariate and p values were HB-adjusted for two comparisons; pairwise comparisons were performed and p values were HB-adjusted.

To examine the relationship between LZC and signal power, the standardized regression coefficient was obtained for the longitudinal regression of LZC on signal power. The regression was done by fitting a GEE model with an unstructured working correlation matrix to the data of the three drug conditions transformed into composite Z scores.

Effect of Drug Condition on Behavioral Measures. Each PANSS factor score exhibited floor effects and positive skewness in the placebo condition. Thus, a nonparametric method was used (54) and the resulting p values were HB-adjusted for three comparisons (one per PANSS factor). For this method, the data were ranked and fitted with a mixed effects model using dose as within-subject factor and an unstructured variance-covariance matrix; p values were adjusted for analysis of variance type statistics. Pairwise comparisons (three per measure) were performed and p values were HB-adjusted for nine comparisons. These analyses were performed with the nparLD package (55) for R 2.14.2 (R Foundation for Statistical Computing, Vienna, Austria) (56).

Relationship Between EEG and Behavioral Measures. To characterize the relationship between Δ^9-THC-induced changes in EEG measures (LZC and signal power) and PANSS factors, standardized regression coefficients (βs) were obtained for the longitudinal regression across both Δ^9-THC-active conditions of each PANSS factor score on each EEG measure (controlling and not controlling for the other EEG measure) with a significant main effect of drug (three coefficients per EEG measure). The p values of the regression coefficients were HB-adjusted for nine comparisons (Supplement 1).

RESULTS

Demographic information is reported in Table 1. Of the 56 subjects who were consented, 10 failed the screening process, 8 never initiated, 8 dropped out before completing, and 30 completed all 3 test days. Due to technical difficulties during EEG acquisition, six completers were excluded from the analyses; in addition, one subject from the .015 mg/kg condition and one subject from the .03 mg/kg condition were excluded from analysis due to artifactual contamination in the preprocessed EEG data. Thus, a total of 24 subjects in the placebo condition and 23 subjects in both the .015 mg/kg and .03 mg/kg conditions were included in the analyses. As reported elsewhere, five nonserious and no serious adverse events occurred on test days (44). For parsimony, statistics are reported either in the text or tables but not both.

Effect of Drug Condition on EEG Measures

Lempel-Ziv Complexity. There was a significant effect of drug condition on LZC (Wald $\chi^2_2 = 42.696$, $p_{Adj} < .001$) that

Table 1. Sample Demographics

General Characteristics	
Number male (female)	17 (7)
Age, mean (SD)	26.208 (8.108)
Handedness	1 left-handed
Years of education, mean (SD)	15.167 (2.014)
Estimated IQ, mean (SD)	115.750 (4.416)
Cannabis Exposure	
Age of first cannabis use	17.000 (2.523)
Days since last use/last exposure, mean (SD) range	445.688 (846.645), 1–3650
Total years of use, mean (SD) range	7.094 (4.486), 1–15
Frequency of cannabis use within past 30 days	Number of Subjects
0 days	12
1–3 days	4
4–8 days	3
9–15 days	3
16–29 days	2
Lifetime cannabis use (total number of exposures)	Number of Subjects
1–10	4
11–50	8
51–200	3
201–500	3
501–1000	3
>1000	3
Cannabis exposure during heaviest use (number of exposures)	Number of Subjects
<1 to 1 per year	6
1 per 3-6 months	4
1-3 per month	3
1-2 per week	2
3-6 per week	5
7 per week	4
Other Drug Exposure	
Daily cigarette smokers (number of subjects)	2
Average number of alcoholic drinks per week, mean (SD)	6.01 (6.06)
Previous recreational exposure to illicit drugs other than cannabis	Number of Subjects
None	11
Hallucinogens	12
Stimulants	10
Opiates	3
Inhalants	2

None of the subjects met criteria for abuse or dependence of the above illicit substances.

remained significant (Wald $\chi^2_2 = 36.319$, $p_{Adj} < .001$) after controlling for signal power. These findings persisted despite HB-adjustment for two comparisons. The six HB-adjusted pairwise comparisons performed before and after controlling for signal power (three comparisons each) revealed significantly higher LZC for the .03 mg/kg (both $p_{Adj} < .001$) and .015 mg/kg ($p_{Adj} < .001$ and $p_{Adj} = .002$, respectively) doses compared with placebo and for the .03 mg/kg dose compared with the .015 mg/kg dose (both $p_{Adj} < .001$) (Figure 1; Table 2).

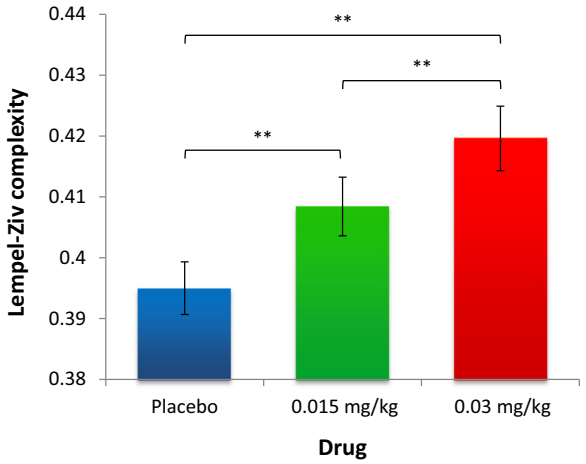

Figure 1. Lempel-Ziv complexity per drug condition. The graph shows the mean and standard error bars of Lempel-Ziv complexity (raw values, not corrected for signal power) per drug condition. Significant differences ($p < .001$) between conditions are indicated with **.

Signal Power. There was a significant effect of drug condition on signal power (Wald $\chi^2_2 = 8.004$, $p_{Adj} = .036$), which disappeared after controlling for LZC (Wald $\chi^2_2 = 2.236$, $p_{Adj} > .1$). Three HB-adjusted pairwise comparisons performed on the data before controlling for LZC revealed significantly lower power for the .03 mg/kg and .015 mg/kg doses compared with placebo (both $p_{Adj} = .029$) but no difference between the .03 mg/kg and .015 mg/kg doses ($p_{Adj} > .1$) (Figure 2; Table 2).

Relationship Between LZC and Signal Power. The regression of LZC on signal power revealed a significant inverse relationship between both variables ($\beta = -.544$, Wald $\chi^2_1 = 42.229$, $p < .001$).

Effect of Drug Condition on Behavioral Measures

The nonparametric analyses HB-adjusted for three comparisons revealed a significant effect of drug condition for the PANSS positive (analysis of variance type statistic [ATS] [1.864] = 28.147, $p_{Adj} < .001$), disorganization (ATS [1.660] = 26.555, $p_{Adj} < .001$), and negative (ATS [1.914] = 12.608, $p_{Adj} < .001$) symptoms factors. The nine HB-adjusted pairwise comparisons showed significantly higher scores for the .03 mg/kg and .015 mg/kg doses compared with placebo (all $p_{Adj} < .001$ except $p_{Adj} = .031$ for the .015 mg/kg dose versus placebo comparison of the negative factor) and for the .03 mg/kg dose compared with the .015 mg/kg dose (all $p_{Adj} < .02$) (Table 2).

Relationship Between EEG and Behavioral Measures

The regressions of the PANSS factor scores on LZC revealed significant HB-corrected (nine comparisons) coefficients for the positive symptoms factor before ($\beta = .442$, Wald $\chi^2_1 = 9.114$, $p_{Adj} = .015$) (Figure S2A in Supplement 1) and after ($\beta = .685$, Wald $\chi^2_1 = 39.419$, $p_{Adj} < .001$) (Figure 3A) controlling for signal power and for the disorganization symptoms factor before ($\beta = .646$, Wald $\chi^2_1 = 15.819$, $p_{Adj} < .001$) (Figure S2A in Supplement 1) and after ($\beta = .754$, Wald

Table 2. Δ^9-THC Effects on Electroencephalographic and Behavioral Measures

Measure	Placebo Mean (SD)	.015 mg/kg Mean (SD)	.03 mg/kg Mean (SD)
Lempel-Ziv Complexity	.395 (.021)	.408 (.023)	.420 (.025)
Total Signal Power	64.391 (32.448)	55.088 (23.082)	54.507 (21.643)
PANSS Positive Factor	6.833 (2.334)	9.435 (2.936)	11.217 (2.999)
PANSS Disorganization Factor	11.667 (2.353)	14.304 (3.183)	16.739 (4.223)
PANSS Negative Factor	7.208 (2.395)	8.870 (3.348)	11.826 (4.579)

Δ^9-THC, delta-9-tetrahydrocannabinol; PANSS, Positive and Negative Syndrome Scale.

$\chi^2_1 = 25.861$, $p_{Adj} < .001$) (Figure 3B) controlling for signal power. No significant coefficients were found for the regression of the negative symptoms factor on LZC (all $p_{Adj} > .1$). In contrast to LZC, no coefficient reached significance for signal power after HB correction ($p_{Adj} > .1$).

Exploratory analysis to determine whether recent (30-day) cannabis exposure influenced the effects of Δ^9-THC on LZC revealed no significant effects of cannabis exposure (Supplement 1). Finally, plasma levels of Δ^9-THC and its metabolite Δ^9-THC-COOH were sampled periodically (Supplement 1), showing a dose-dependent increase as reported previously (44).

DISCUSSION

To our knowledge, this is the first study to demonstrate an increase in neural noise, defined as the randomness of EEG signals, induced by a psychotomimetic drug in humans. More specifically, this study showed for the first time that Δ^9-THC increased neural noise indexed by LZC in a dose-related manner. As expected [reviewed in (24–26)], Δ^9-THC increased positive, disorganization, and negative symptoms. Furthermore, there was a strong positive relationship between neural noise and the psychosis-like effects induced by Δ^9-THC, which was independent of the changes in total signal power. In contrast, there was no relationship between noise and negative-like symptoms. This suggests a specific relationship between neural noise and Δ^9-THC induced psychosis-like effects, raising the intriguing possibility that neural noise may be involved in other forms of psychosis as well. In addition, Δ^9-THC reduced total signal power during both active drug conditions compared with placebo, but this effect disappeared after controlling for LZC. No relationship was detected between signal power and psychosis-like symptoms. Finally, an inverse relationship between LZC and signal power was observed.

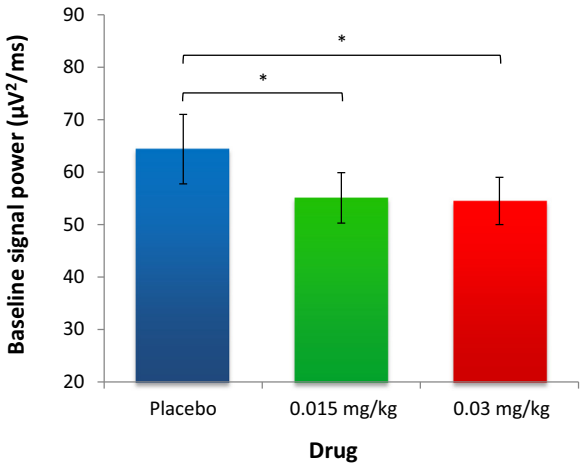

Figure 2. Baseline signal power per drug condition. The graph shows the mean and standard error bars of baseline signal power (raw values, not corrected for Lempel-Ziv complexity) per drug condition. Significant differences ($p < .05$) between conditions are indicated with *.

Noise and Signal Power

As described above, LZC is a nonlinear measure of the randomness (noise) of time series (30). While Δ^9-THC increased noise in a dose-dependent manner, the signal did not become completely random, a state that would be associated with an LZC value of 1. Note that the LZC value associated with a perfectly regular (periodic) or predictable signal would approach 0 (31,32). What the associated LZC value is for optimal brain function remains unknown and is likely an intermediate value between 0 and 1.

Animal studies have revealed that cannabinoids acutely reduce the spectral power of LFP oscillations by increasing the randomness (reducing the synchronization) of the activity of populations of neurons rather than reducing the activity of individual neurons (28,29). The increased randomness would reduce the neurons' capacity to form temporally coordinated ensembles, leading to a reduction of LFP spectral power (28). Consistent with these findings, our results showed that Δ^9-THC reduced signal power and increased randomness and that there was an inverse relationship between signal power and randomness.

Relationship Between Noise, Connectivity, and Behavior

As discussed above, keeping the bandwidth and total power of a signal constant, the higher the level of random noise, the lower the amount of information that can be carried by a signal without distortion. Considering that our findings were independent of total signal power and that the bandwidth of the signals was kept constant (99.5 Hz) across conditions by filtering, we speculate that our findings could reflect a negative relationship between the amount of error-free information capable of being carried by the brain signals and the psychosis-like effect induced by Δ^9-THC. Furthermore, we hypothesize this may affect the capacity of different brain areas (nodes) to process information coordinately. This would, of course, apply only to the brain sources captured by the midline electrodes used in our analyses. However, if the

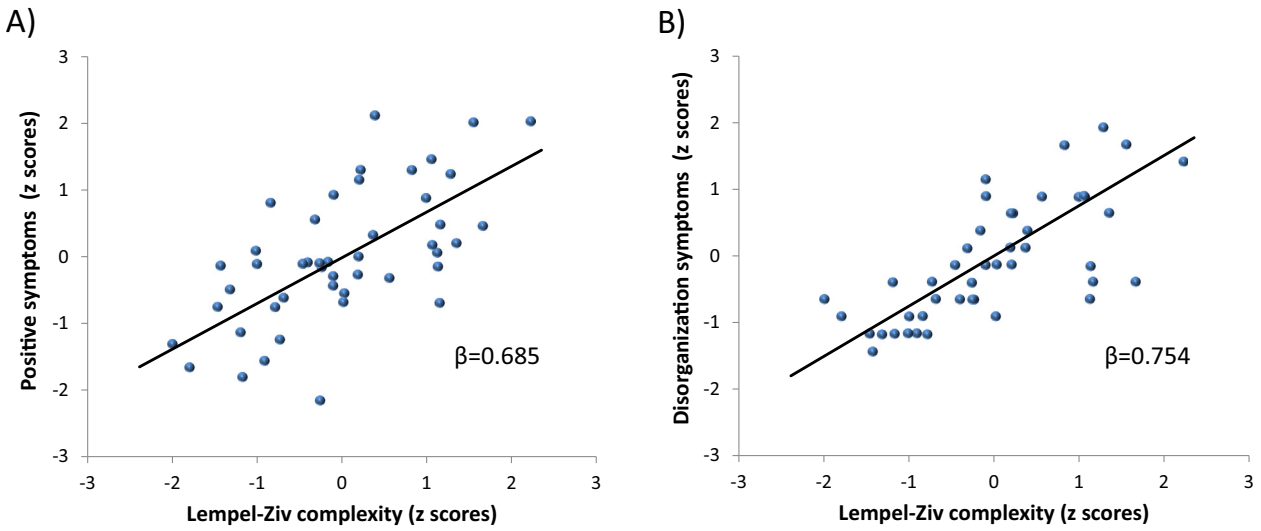

Figure 3. Delta-9-tetrahydrocannabinol induced positive and disorganization symptoms versus Lempel-Ziv complexity (LZC) corrected for signal power. The figure shows the regression lines and standardized coefficients of the regressions of positive **(A)** and disorganization **(B)** symptom factors of the Positive and Negative Syndrome Scale on LZC corrected for signal power. Positive and Negative Syndrome Scale scores and LZC values are presented in *Z* scores.

activity captured by these electrodes is representative of the activity within larger brain areas, then one might speculate that the results of this study may be informative about brain function in general. If so, these results would be aligned with some theoretical models proposing an aberrant connectivity (dysconnection) between brain areas as the underlying mechanism of psychotic symptoms in schizophrenia (57–59). Furthermore, we speculate that LZC will be inversely correlated to electrophysiological indices of connectivity such as phase lag index (60) and inter-electrode coherence (61).

Mechanism of Noise

While it is beyond the scope of this study to determine the mechanism by which Δ^9-THC increased noise, it is tempting to speculate on some explanations. In the cerebral cortex and hippocampus, CB1Rs are located on the axon terminals of cholecystokinin-expressing gamma-aminobutyric acidergic interneurons (62). While parvalbumin-expressing gamma-aminobutyric acidergic interneurons seem to have the main role in the generation of regular oscillatory activity (nonrandom recurrent patterns), it has been proposed that cholecystokinin cells enhance the signal-to-noise ratio of neural oscillations (like a noise filter) through a CB1R-mediated mechanism (63–65). Thus, it may be the case that the observation that Δ^9-THC increased LZC resulted from a disruption of this noise filter mechanism by the nonphysiologic activation of CB1Rs by Δ^9-THC. While the manner in which this abnormality would affect neural computations is far from being clear, it is interesting to note that increased levels of LZC and similar measures have been reported in schizophrenia and have been related to periods of symptomatic exacerbation (21–23).

LZC Complements Traditional Measures of Brain Activity

Event-related potentials are one of the EEG measures most widely used in current studies of psychoses. Event-related potentials provide valuable information about the consistency and strength of the brain's time-locked response to different presentations of a stimulus. Using this approach we showed that Δ^9-THC reduced the amplitude of the P300 (44). LZC complements these measures by capturing a different aspect (randomness) of the neural dysfunction underlying Δ^9-THC-induced psychosis-like symptoms. Interestingly, exploratory analyses revealed medium-sized ($\beta \approx -.4$) negative relationships between LZC and the amplitudes of P3a and P3b. Of note, while P3a or P3b amplitudes were not related to symptoms measured either by the three-factor (44) or five-factor (current) solution of the PANSS, LZC was related (Supplement 1). Furthermore, we explored the relationship between baseline power (an index of brain activity not evoked by a task) in the traditional frequency bands and psychosis-like symptoms. Similar to the Spencer (43) study on schizophrenia patients, we found no relationship between baseline power and psychosis-like symptoms in any frequency band (Supplement 1). Taken together, these findings suggest that LZC may be more sensitive to the pathophysiology underlying positive symptoms than some traditional EEG measures. Thus, LZC may be able to provide information about the pathophysiology of positive symptoms that has been overlooked by studies using these measures.

Strengths and Limitations

Unlike other measures of noise (e.g., intertrial variability, increased task-unrelated activity) (14–18,39,43), LZC provides direct information about the level of randomness of the EEG signals (30), which makes it more suitable for quantifying the noise of brain activity. The obvious differences between these measures limit any direct comparisons between the results of this study and those previously obtained in schizophrenia.

In contrast to previous evoked-response studies (14–18, 39), in this study, data captured immediately before the onset of the stimulation period were analyzed. Despite the fact that

the prestimulation period does not capture evoked activity, it is not true resting state activity due to the anticipation elicited by recurring events (i.e., auditory click trains) and the expectation associated with task-related stimuli (i.e., P3b). Thus, whether our findings apply to resting state activity or to activity associated with expectancy during the prestimulation will need to be determined in future studies.

In this study, continuous EEG data were transformed into binary symbolic sequences using the threshold-crossing approach (Methods and Materials) before calculating LZC. While this approach is associated with some loss of information (66,67) about the fine-grained dynamics of the system generating the signals (e.g., the brain), it is capable of providing an accurate representation of the macroscopic-level dynamics of the system (67). Furthermore, a consequence of using the median as the threshold is that low-range frequencies are preferentially represented in the resulting binary data (Supplement 1). Even though the median-crossing approach is widely used, alternate approaches [e.g., (68)] that better represent the entire frequency spectrum should be explored. The loss of some information notwithstanding, LZC based on this approach has been informative about the brain in health and disease (34,35,37,38).

Conclusions

At doses that produced increases in psychosis-like effects, Δ^9-THC increased neural noise (LZC) measured in the EEG of humans in a dose-dependent manner. Furthermore, increases in neural noise were positively related with Δ^9-THC-induced psychosis-like, but not negative-like, effects. These findings suggest that neural noise may contribute to the psychotomimetic effects of Δ^9-THC. Further replication of these findings is warranted as are studies into the mechanisms underlying the increases in neural noise (e.g., studying the intracortical correlates of these surface recordings in animals). It would be interesting to determine whether these findings are exclusive to Δ^9-THC or whether other drugs known to produce psychosis-like effects (e.g., ketamine [NMDA receptor antagonist] and psilocybin [serotonin 2A receptor agonist]) increase LZC and whether the drug-induced increases in LZC correlate with psychosis-like effects. While LZC is increased during decompensation (22), to our knowledge, whether LZC is correlated with psychotic symptoms in schizophrenia patients has not been studied. If confirmed, LZC may have significant utility as a novel biomarker for the functional deficits underlying psychotic symptoms. Finally, while admittedly speculative, if psychotic symptoms are a result of brain dysconnectivity related to an abnormal increase of neural noise, interventions directed toward reducing noise may have therapeutic potential.

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WORK 4

As an example of this sort of analysis, Fig. 3 shows the results of MSI performed on 4 separate spikes, each differing slightly in terms of topography or amplitude. Despite the high goodness-of-fit values for each of the source solutions, the dipole localizations are scattered rather unpredictably within the temporal lobe.

It is perhaps a testament to how far the field has advanced that we are able to solve the inverse problem with even this degree of lobar accuracy. But it is not unreasonable to attempt to achieve even better, more consistent, localization results. Rigorous studies comparing dipole source solutions with their actual intracranial fields represent a logical and necessary progression in electromagnetic source imaging research. Recent advances facilitating the simultaneous recording of MEG and intracranial EEG promise even greater insights into the nature of dipole variability in MEG/MSI.

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Testing differences in the activity of event-related potential sources: Important implications for clinical researchers

Source analysis of electroencephalographic (EEG) data is an increasingly popular tool that allows investigators to estimate the location, direction, and strength of the electric currents within the brain. Clinical researchers have increasingly exploited user-friendly Linear Distributed Source Model (LDSM) software packages (such as sLORETA-KEY) to extend classical event-related potential (ERP) experiments. However, methodological biases and inferential errors may have occurred. Spatial solutions tend to be accurately reported, but, use of standard methods to quantify source activity can introduce error into group/condition comparisons of "ERP generators", especially when the experimental effect is hypothesized to alter ERP peak amplitude or latency. Since 2010 alone, this journal has published a number of clinical studies reporting source localization of ERPs in which one cannot exclude one or more of these methodological or inferential issues (outlined in Table 1). We illustrate the potential pitfalls with proposed solutions.

In LDSMs-based analyses, either cortical grey matter is divided into a number of voxels or cortical surface is modeled as a mesh with a number of vertices, each of which is assigned a three dimensional vector representing electric activity (EAV), a current density vector in the first case, or an electric dipole in the second. The length (norm) and orientation of an EAV correspond, respectively, to the magnitude and direction of flow of the reconstructed current (Pascual-Marqui, 2002). Grossly, positive scalp potentials would result from currents flowing towards scalp sensors, whereas negative scalp potentials would result from currents flowing away from these sensors.

As EEG signals are purported to result from the summed field potentials generated by cortical neurons whose dendritic trees are perpendicular to the cortical surface, EAVs are frequently constrained to be oriented in this direction (Grech et al., 2008). To facilitate statistical comparison and graphical representation, it is common to then reduce each EAV (possessing three values per voxel or vertex) to its norm ($|x|$, a single positive number). Consequently, information about the direction of flow of current is lost. The norm solution, favored by popular software packages, is therefore not a complete reconstruction of the activity underlying the signals recorded at the scalp; instead, it only yields the magnitude of the activity. Although a perfectly valid measure in itself, source magnitude may be insensitive to some facets of underlying neural processes and cannot be directly related to the scalp ERPs.

A temporal window centered on the peak of the scalp ERP is defined. Sources at each time point within this window are reconstructed and averaged across time to yield what is interpreted as the 'ERP source'.

1. Issue 1: Testing differences in ERP peak amplitude and source activity

A group/condition difference in the norm solution informs us that cortical areas coincidently active with the ERP peak have different magnitude. However, this does not prove a difference in cortical activity 'underlying' or 'generating' the ERP directly. If aiming to draw inferences about cortical activity that directly contributes to the ERP, the use of the norm solution is analogous to comparing scalp-ERPs using the absolute value of their peak amplitude (Fig. 1A).

A rich literature describes a range of clinical states in which the amplitude of ERPs is diminished (Folmer et al., 2011; Polich and Criado, 2006; Thaker, 2008; Turetsky et al., 2007). ERP amplitudes are commonly utilized as dependent measures in studies examining the neural basis of cognitive function (Bartholow, 2010; Kotchoubey, 2006; van Veen and Carter, 2002). Under certain experimental conditions, amplitude perturbation may impede an individual's ERP from even crossing the temporal axis (Fig. 1A). Thus, the value of that ERP peak, and hence source activity, would possess an opposite sign than characteristically expected. If the norm solution is then taken, the amplitude perturbation is erroneously diminished and some variance perhaps attributable to an experimental effect is lost, even when a robust difference in ERP peak amplitude exists at the scalp and the sources

Table 1
Clinical studies reporting source localization of ERPs which may be prone to methodological or inferential issues.

References	Potential problems due to...		
	Issue 1	Issue 2	Inferential language
Babiloni et al. (2009)	Yes	–	"amplitude of prefrontal P300 sources..."
Doege et al. (2010)	Yes	–	"ERP components and their source localisation"
Jung et al. (2010)	Yes	–	"current density of P200 component was significantly reduced..."
Babiloni et al. (2011)	Yes	–	"...P300 sources..."
Fisher et al. (2011)	Yes	Yes	–
Tanaka et al. (2012)	Yes	Yes	"N1 source"
De Pascalis et al. (2013)	Yes	Yes	–
Annic et al. (2014)	Yes	–	"...cortical generators of the N100 and P200 components..."

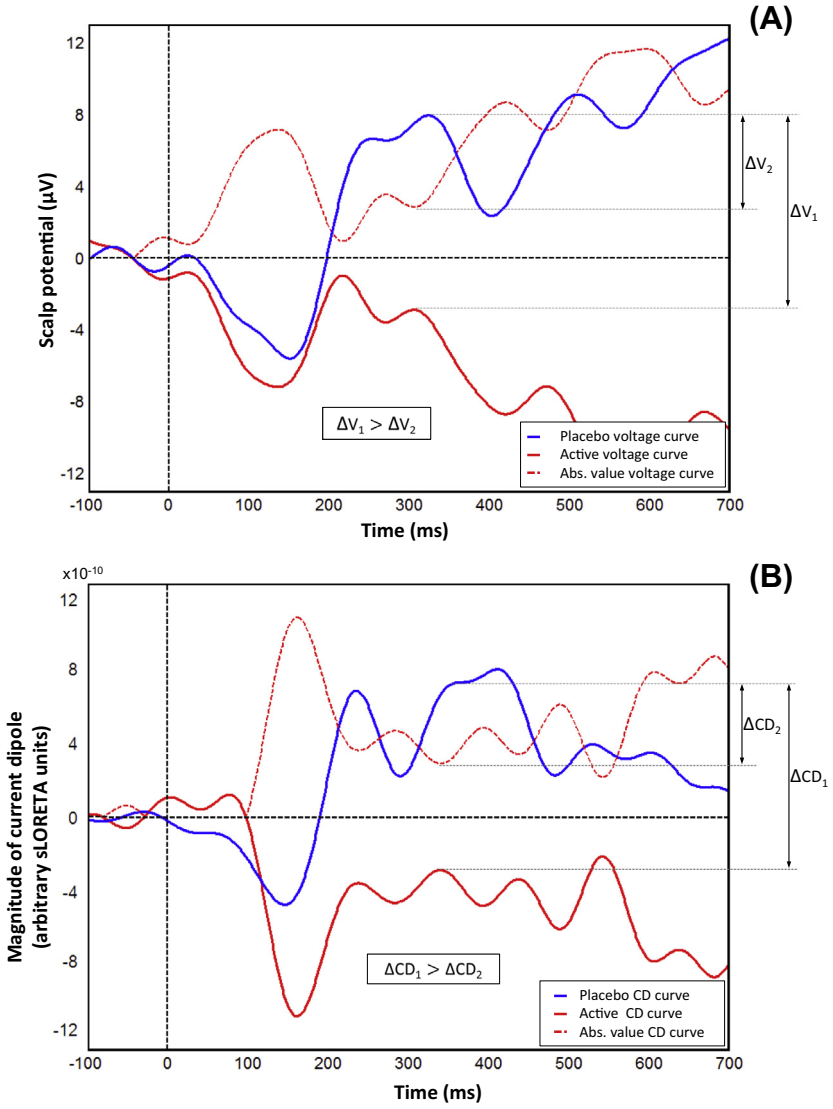

Fig. 1. (A) This figure shows the P3b ERPs at electrode CPz of a representative subject from our lab receiving either placebo (blue curve) or an active drug (red curve), and the absolute value of the ERP of the active drug condition (red dashed curve) (for the methods, see (D'Souza et al., 2012)). It illustrates the case when the reduction of an ERP's amplitude impedes it from having its expected polarity. This abnormality is reflected in the comparison of the peak amplitudes as a large voltage difference between the conditions (ΔV_1). Instead, a comparison based on the absolute value of the voltage is not able to capture it: it reduces the difference between these highly dissimilar ERPs to a small 'ordinary' value (ΔV_2). This is analogous to the case when the sources of the different conditions are compared using the norm solution instead of the vector solution (B). Processing and source analyses of the data shown in all the figures were done using custom scripts and the Brainstorm toolbox (Tadel et al., 2011) for Matlab (MathWorks). (B) The figure shows the time course of the magnitude of a current dipole (CD) perpendicular to the cortex of a point located in the temporo-parietal area (one of the generators of the P3b (Polich, 2007)) during the occurrence of ERPs depicted in (A); it also shows the norm solution of the ERP of the active condition (red dashed curve). Analogous to what occurs with the EEG signals (A), the activity of the placebo (blue curve) and the active (red curve) conditions have different polarities during the occurrence of the ERP. In the comparison of the peaks this abnormality is reflected as a large difference between the magnitude of the current dipoles of the conditions (ΔCD_1); instead, under the norm solution the difference between these highly dissimilar conditions appears to be small (ΔCD_2).

(Fig. 1A and B). Analyzed within a dataset, such data-points may theoretically increase the risk of missing empirically relevant differences between the sources' activity of the groups/conditions. Furthermore, the loss of variance may also theoretically increase the risk of finding differences that may have little to do with the between-group/-condition differences of ERPs. All studies utilizing these methods, published and unpublished, must discuss or avoid this potential bias.

In an attempt to make group/condition comparisons of the norm solution, some investigators localize the between groups/conditions ERP difference wave. This raises its own inferential challenges, beyond the scope of this letter.

The norm solution treats source current moving towards and away from the scalp as equal. Although theoretically valid, the description of sources as ERP "generators" or "contributors" loses meaning when they are described in terms of the norm solution alone. Such terms imply a direct relationship, whereas, given a decrease in ERP peak amplitude, the norm solution of an individual's source may decrease, increase, or stay the same.

2. Issue 2: Studies where differences in ERP Peak Latency may exist

Shifts in the latency of certain ERPs are known to occur in several neuropsychiatric disorders (e.g. schizophrenia patients) and with drug administration (e.g. benzodiazepines or nicotine) (Jeon and Polich, 2003; Lucchesi et al., 2005; Pritchard et al., 2004; Urata et al., 1996). When comparing the magnitude of source activity, many investigators account for ERP latency

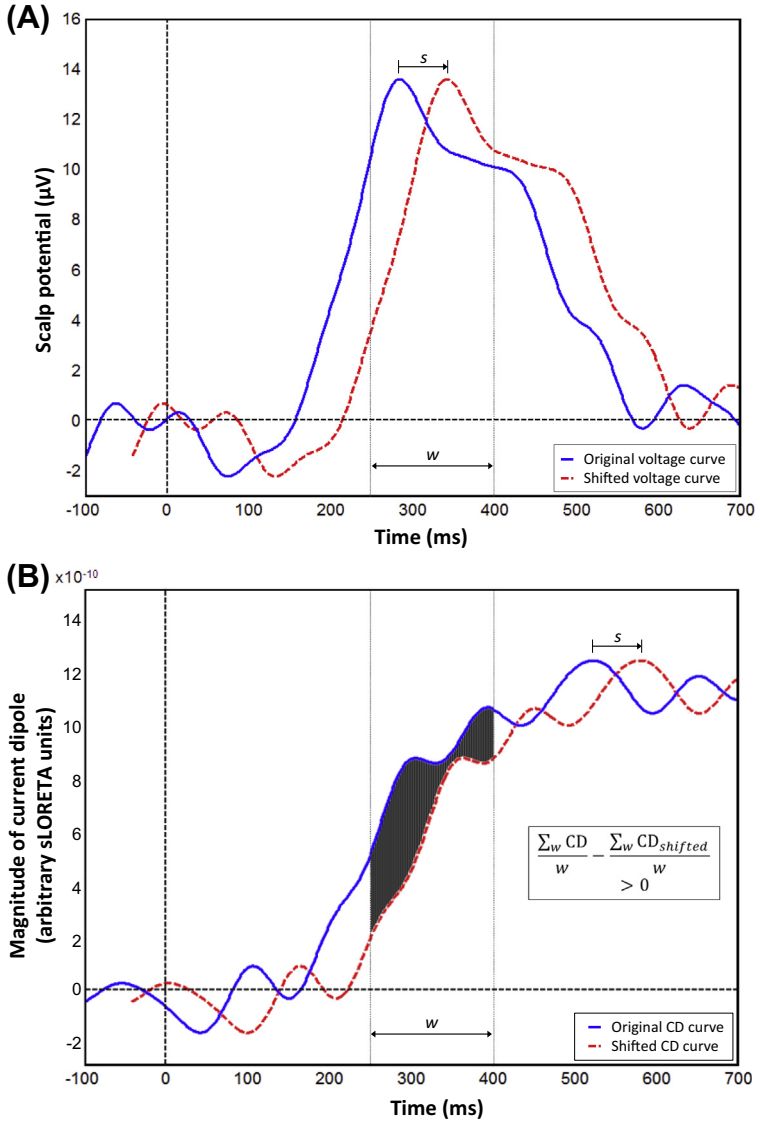

Fig. 2. (A) The figure shows two identical P3b ERP curves at CPz one of which has been shifted '*s*' milliseconds in time. It represents the scenario when comparing groups/conditions in which one has a peak latency shift compared to the other. The same ERP curves were used for both cases to highlight the consequences resulting only from the time shift without the intervention of other variables (see (B)). Blue curve: P3b ERP at electrode CPz of a representative subject from our lab obtained by averaging across trials (methods describes in (D'Souza et al., 2012)). Red dashed curve: the same ERP but shifted in time. '*w*': length of the common interval used to capture the ERP's peak in both conditions. (B) The figure shows the time course of the magnitude of a current dipole (CD) perpendicular to the cortex of a point located in the temporo-parietal area (one of the generators of the P3b (Polich, 2007)) during the occurrence of the shifted (red curve) and non-shifted (blue curve) ERPs depicted in (A). The hatched area shows the difference between the activities of both conditions during the common analysis interval '*w*'. The shift introduces a difference between the conditions that is not coming from the magnitude of the sources' activity (both sources have the same curve) but from the peak latency difference existing between them.

variation by defining temporal windows centered on the ERP peak for each individual, in each condition/group. Issues may arise however when the same temporal window is applied to all groups/conditions.

Due to latency shifts, the neural sources of individuals belonging to different groups/conditions obtained with the averaged-interval technique may reflect very different moments of the ERP waveform (Fig. 2A). This may generate between-group/-condition differences in the magnitude of the reconstructed sources' activity that disappear after correcting for the latency shift effect (Fig. 2B). Furthermore, significant differences in source magnitude that occur between groups/conditions, within classical ERP temporal windows, are not necessary relatable to neural processes that underlie the coincident ERP.

In summary, LDSM software packages offer valuable and increasingly accessible tools for localization of the electrical activity associated with ERPs. These techniques promise to expand our understanding of ERPs. However, caution must be exercised when attempting to integrate ERP source activity findings into classical ERP approaches. We highlight a set of potential issues, now emerging with the expanding use of these techniques, particularly in clinical research. Investigators should be mindful of the distinction between source magnitude and activity and choose the more appropriate measure for testing their hypothesized effect.

As a general rule, when seeking to infer differences in cortical activity related to an ERP, we suggest investigators: (1) Consider using the vector (non-norm) solution; (2) Identify an ERP peak window for each subject individually. If the norm solution is used, it may be more accurate to interpret the source magnitude as coincident with rather than either directly related to, or a "generator" of the ERP.

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Compatibility of intraoperative 3 T MR imaging and intraoperative neurophysiological monitoring

One of the main challenges in brain tumor surgery is achieving the largest extent of resection (EOR) possible without causing damage to the surrounding healthy brain parenchyma. This is especially difficult in tumors which cannot be distinguished from normal brain reliably with the operating white light microscope and in lesions in close proximity to eloquent areas. EOR is linked to survival (Kreth et al., 2013) and much effort has been invested in the development of technologies that guide tumor resections in order to improve EOR. In daily practice, intraoperative neurophysiological monitoring (IONM), neuronavigation, intraoperative magnetic resonance imaging (ioMRI), intraoperative ultrasound (ioUS) and 5-aminolevulinic acid (5-ALA) are the most frequently used ones. IONM helps the surgical team to monitor neural function (Macdonald et al., 2013). Neuronavigation using preoperative contrast-enhanced MRI images helps to identify tumor, but brain shift occurring during resection often makes the preoperative

WORK 5

American Society of Clinical Psychopharmacology Corner
J Craig Nelson, MD, Editor

The Endocannabinoid System and Schizophrenia: Links to the Underlying Pathophysiology and to Novel Treatment Approaches

Swapnil Gupta, MBBS, MD; John D. Cahill, MBBS; Mohini Ranganathan, MD; and Christoph U. Correll, MD

Six decades after the introduction of dopamine D2-receptor–based antipsychotics, schizophrenia remains one of the most severe and difficult-to-treat mental disorders. While a range of alternative therapeutic targets, such as the glutamatergic system, have attracted attention for negative symptoms and cognitive dysfunction,[1] novel treatments for the core symptoms of schizophrenia remain unproven.[2]

The Endocannabinoid System

The endocannabinoid system (ECS) is a largely overlooked brain homeostatic system that is relevant to both the pathophysiology and treatment of schizophrenia. It centers on 2 G-protein–coupled receptors, cannabinoid-1 receptor[3] and cannabinoid-2 receptor[4]; lipid ligands or endocannabinoids[5,6] including anandamide and 2-arachidonoylglycerol; and enzymes involved in endocannabinoid biosynthesis (diacylglycerol lipase) and degradation (fatty acid amide hydrolase [FAAH] and monoacylglycerol lipase).[7,8] Cannabinoid-1 receptors are highly expressed in the brain regions implicated in the putative neural circuitry of schizophrenia, including the cerebral cortex, basal ganglia, hippocampus, anterior cingulate cortex, and cerebellum,[9] where they modulate presynaptic glutamate and GABA release.[10,11] Furthermore, endocannabinoids enhance dopaminergic function in the prefrontal cortex and hippocampus while providing inhibitory feedback on mesolimbic dopamine neurotransmission.[12–14] Finally, endocannabinoids are increased in response to stress, possess intrinsic antioxidant properties, and are precursors of membrane lipids, leukotrienes, and prostaglandins.[15]

The Endocannabinoid System and Schizophrenia

Anandamide levels, increased in acute schizophrenia, may represent a compensatory mechanism, specifically in early illness. Cerebrospinal fluid and plasma levels of anandamide were noted to be significantly increased in acutely ill, antipsychotic-naive, first-episode schizophrenia patients compared to controls.[16,17] Increased levels negatively correlated with psychotic symptoms and normalized with antipsychotic response.[17] Furthermore, in prodromal individuals, elevated anandamide levels were associated with lower risk of conversion to schizophrenia,[18] suggesting that anandamide increases could be compensatory in this context.

Studies of cannabinoid-1 receptor densities in schizophrenia show mixed results. Postmortem studies of cannabinoid-1 receptors in schizophrenia have found alterations in the anterior[19] and posterior[20] cingulate cortices, but 1 study[21] found no changes. The availability of positron emission tomography (PET) ligands for in vivo imaging techniques shows promise for future studies.[22] In a preliminary PET study in schizophrenia patients, Wong et al[23] found that elevated cannabinoid-1 receptor density in the frontal, middle, and posterior cingulate regions correlated with psychopathology.

Cannabinoid-1 receptor gene polymorphisms may be associated with schizophrenia. Cannabinoid-1 receptor gene[3] (*CNR1*) polymorphisms have been associated with schizophrenia in some studies,[24,25] but not in others.[26,27] While this inconsistency might reflect demographic differences in the study populations, another possibility is the heterogeneity of the illness.

Exogenous Cannabinoids and Schizophrenia

Epidemiologic studies have linked both onset and extent of cannabis use with the development and severity of schizophrenia. A number of longitudinal studies have found that earlier onset of cannabis use, especially before 18 years of age, was associated with an increased incidence of psychotic symptoms or disorder later in life.[28–31] For instance, a study of Swedish military conscripts (N = 45,570) showed a significant dose-response relationship between self-reported cannabis use at enrollment and psychiatric hospitalization for schizophrenia in the ensuing 15 years.[28] Heavy cannabis users by 18 years of age were 6.7 times more likely than nonusers to be hospitalized for schizophrenia later in life.[29] Similarly, a birth-cohort study of 1,037 people born in Dunedin, New Zealand,[30] found that, compared to nonusers, individuals with cannabis use at ages 15 and 18 years had higher rates of psychotic symptoms and schizophreniform disorder at age 26. Consistent with these studies, a systematic review[32] of 35 studies demonstrated an increased risk of psychosis in individuals who had ever used cannabis and the existence of a dose-response effect, with greater risk in people who used cannabis most frequently. Meta-analyses of studies of cannabis use and psychosis suggest that cannabis is a component cause in the development and prognosis of psychosis[33] and that the age at onset

of psychosis was 2.7 years earlier among cannabis users compared with non–substance-using controls.[34] Finally, in a recent nationwide Finnish study,[35] the 8-year rate of ultimate conversion to schizophrenia in 18,478 patients with substance-induced psychotic disorders was highest in cannabis users (46%), followed by amphetamine (30%) and alcohol (5%) users. Moreover, the risk was highest in the first 3 years, especially in cannabis users.

Δ9-tetrahydrocannabinol, a partial cannabinoid-1 receptor agonist, produces psychotomimetic effects, whereas cannabidiol, a putative FAAH inhibitor, may attenuate them. Cannabis contains a number of constituent cannabinoids of which Δ9-tetrahydrocannabinol (THC) is the main psychoactive component. In psychopharmacologic challenge studies, the acute administration of THC has been shown to transiently induce a range of positive, negative, cognitive, and psychophysiologic abnormalities in healthy people, comparable to those observed in schizophrenia.[36] THC similarly induced an increase in psychotic symptoms in stable, antipsychotic-treated schizophrenia patients, who were more sensitive to THC-induced positive symptoms and cognitive deficits as compared to healthy controls.[37]

In contrast to THC, cannabidiol, another component of cannabis, does not appear to have psychotomimetic effects, instead producing hypnotic, anticonvulsive, anxiolytic, and neuroprotective effects.[38] In healthy subjects, cannabidiol pretreatment reduced the psychotomimetic effects of THC[39] and attenuated ketamine-induced depersonalization.[40] Furthermore, chronic cannabis users with evidence (per hair analyses) of significant cannabidiol exposure showed lesser positive schizophrenia-like symptoms than those without.[41]

Conversely, a subgroup of schizophrenia patients may derive benefit from exogenous cannabinoid-1 receptor agonism. Despite the above evidence, cannabis continues to be the most-abused illicit substance in schizophrenia.[42] In 1 open-label study,[43] treatment with dronabinol resulted in symptomatic improvement in 4 of 6 treatment-resistant patients who had a self-reported history of benefits from cannabis use. Additionally, meta-analysis revealed that in a subgroup of patients, cannabis use is associated with improved cognition,[44] further pointing to a significant heterogeneity in the interaction between the disease and cannabis.

In summary, the ECS is implicated in the major pathophysiologic hypotheses for schizophrenia: mesolimbic hyperdopaminergia (and dopaminergic hypofrontality), glutamate/GABA disruptions, oxidative stress, deficiency of membrane lipids, and neuroinflammation. Its involvement is supported by alterations in the ECS in patients with schizophrenia and further by epidemiologic and laboratory data supporting the role of exogenous cannabinoids in psychosis and schizophrenia. Given the pleiotropism of the ECS and heterogeneity of the evidence, the nature of the link between the ECS and schizophrenia is complex, requiring further study.[45]

Novel Treatment Strategies Based on the Endocannabinoid System

Cannabinoid-1 receptor antagonism has demonstrated anxiolytic but no clear antipsychotic effects. Alternatively, novel therapeutic targets focused on boosting endogenous anandamide levels may show greater promise.[46] Such targets may have most utility in acute, early-phase schizophrenia via their ability to increase prefrontal and decrease mesolimbic dopamine. Elevating anandamide levels has been shown to ameliorate symptoms in animal models of schizophrenia; for example, hyperlocomotion in dopamine transporter knockout mice[12] and PCP-induced social withdrawal.[47] Anandamide itself has poor bioavailability, but drugs exist that reduce its deactivation via inhibition of FAAH and blocking reuptake into the neuron.[48] In a 4-week trial of 42 acute schizophrenia patients, cannabidiol showed comparable efficacy to amisulpride for positive and negative symptoms, while being better tolerated.[49] Moreover, symptom improvement correlated with increases in anandamide, suggesting that cannabidiol may mediate its effect via FAAH inhibition. Synthetic FAAH inhibitors increase anandamide over 2-arachidonoylglycerol levels, the latter of which may be implicated in cannabinoid-1 receptor–mediated psychotic effects. A range of synthetic anandamide-boosting drugs promise efficacy and tolerability in mood and anxiety disorders,[50,51] but these have not yet been tested in schizophrenia.

Future Directions

In vivo cannabinoid-1 receptor imaging. Availability of several cannabinoid-1 receptor PET ligands now permits in vivo imaging in patients at every stage of psychotic illness.[23] Future studies may disambiguate the effects of antipsychotic medications, stage of illness, and cannabis use (among other factors) from schizophrenia-related changes in cannabinoid-1 receptor availability.

Preclinical and clinical studies examining the role of the cannabinoid-2 receptor in schizophrenia. Initial genetic linkage studies associated cannabinoid-2 receptor gene hypofunction with an increased risk of schizophrenia,[52] warranting further study of this association and treatments directed at this receptor.

Acute psychopharmacologic challenge studies in healthy humans. The controlled, acute administration of THC in a laboratory serves to probe the ECS and characterize its role in psychosis. Further, putative therapeutic drugs can be

tested against THC in this laboratory model. Finally, characterizing the relative contributions of the principal constituents of cannabis on psychotomimetic effects may have important public health implications.

Clinical trials of novel ECS agents in schizophrenia. Novel antipsychotic drugs targeting the ECS may best focus on early-phase schizophrenia given a preponderance of clinical evidence in this population. On the basis of the hypothesis that the ECS (perhaps via increases in anandamide) plays a compensatory role in early psychosis, treatment with a FAAH inhibitor could decrease conversion to schizophrenia in prodromal patients or improve prognosis in first-episode psychosis patients.

Conclusions

There are substantial preclinical, clinical, and epidemiologic data supporting the involvement of the ECS in schizophrenia. The ECS hypothesis unifies other major pathophysiologic hypotheses of schizophrenia. Further studies are warranted to further probe the exact nature of ECS abnormalities in schizophrenia. Consideration of stage and heterogeneity of the illness is vital. Further exploration of the potential benefit of cannabidiol and other anandamide-boosting agents may lead to novel treatments.

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WORK 6

A Prescription for "Deprescribing" in Psychiatry

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The term "deprescribing," initially coined in geriatric medicine, describes a process of pharmacologic regimen optimization through reduction or cessation of medications for which benefits no longer outweigh risks. Burgeoning rates of polypharmacy, growing appreciation of long-term adverse effects, and a focus on patient-centered practice present specific indications for deprescribing in psychiatry. A strong therapeutic alliance, appropriate timing, and consideration of the meaning of medication for the patient must accompany the following established elements: review of all medications, identification of medications that could be ceased or reduced, collaborative planning of the deprescribing regimen, and provision of review and support to the patient and caregivers. The authors discuss how deprescribing might be adapted for and implemented in psychiatry, identify potential barriers, and make recommendations for future directions.

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A term now established in geriatric medicine, "deprescribing" has been defined as the systematic process of identifying and reducing or discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits, taking into account the patient's medical status, current level of functioning, and values and preferences (1). The end goal of deprescribing is not necessarily the complete cessation of medications but rather their parsimonious use. Despite a scattered and disparate literature examining dose reduction or discontinuation of maintenance regimens (mostly notably antipsychotics and benzodiazepines), only recently in psychiatry's history have general, structured, multidimensional approaches to medication discontinuation gathered momentum. Similarly, the field of cardiology is questioning the need for long-term medications by critically reexamining the evidence base and developing strategies for repeated risk-benefit analyses over time (2).

Changing systems of care, lack of diagnostic and therapeutic precision, and a focus on symptomatic rather than functional outcomes have conspired with a relative lack of clinical evidence for (or experience with) medication discontinuation to increase rates of "prescribing inertia" and polypharmacy. Furthermore, many psychosocial factors, along with comorbid general medical and substance use disorders and the high importance given to the subjective experiences of patients, yield a particularly complex risk-benefit analysis for psychotropic medications. In this Open Forum, we describe how the process of deprescribing might be implemented in psychiatry, along with potential benefits, challenges, and future directions.

Indications for Deprescribing in Psychiatry

Changing Risk-Benefit Ratio. Biological, psychological, and social factors must align to produce a favorable risk-benefit ratio such that a medication regimen becomes established for a patient. Over time, this risk-benefit ratio can change, providing an indication for deprescribing. Certain adverse effects may develop only after longer-term use—for example, tardive dyskinesia with antipsychotics and renal impairment with lithium. Normal aging alters both the pharmacodynamics and the kinetics of medications, increasing vulnerability to side effects. Pregnancy, the development of general medical comorbidities, new medication interactions, and substance abuse raise similar issues. Psychological factors, such as patients' choice, their understanding of illness and medication, and their coping strategies, may evolve over time, shifting their individual risk-benefit ratio. Social factors, such as geographical relocation, changes in financial and insurance status, and changes in religion, may prompt a reappraisal. The growth of the recovery movement and patient-centered care in psychiatry, including in pharmacological management, further necessitates the development of deprescribing skills.

Nonadherence and Treatment Alliance. Medication nonadherence is a significant and underappreciated issue in all of medicine. Abrupt, unsupervised discontinuation of certain medications risks withdrawal syndromes, rebound effects, and relapse of the underlying condition. Although research has attributed nonadherence to a range of pragmatic as well as treatment-specific factors, the lack of communication between the patient and the prescriber when the patient unilaterally decides to discontinue a medication raises questions of disconnect in the patient-prescriber relationship that are particularly pertinent in psychiatry. Perhaps by showing expertise in collaboration—and a willingness to collaborate—in regard to medication discontinuation from the outset, prescribers may

reduce the chances of this disconnect and improve the alliance. Ambivalence about diagnosis and treatment is prevalent in psychiatry, attributable to the relative proximity of disorders to the core sense of self or to direct effects on insight and judgment. Due to the stigma associated with mental illness, which is often heightened by news media coverage, and an initial treatment focus on remission, a patient's first impression of the psychiatrist may be that of a "pill pusher." Alternatively, a patient may desire to please the prescriber through continued adherence, which might also generate conflict in regard to treatment. An initial discussion that gives equal weight to deprescribing (when appropriate) as well as prescribing may serve to counter such conflict.

Furthermore, guided by the patient's preference, collaboration about a trial reduction or discontinuation of a medication, even if unsuccessful, might enhance the therapeutic relationship and the patient's understanding of the illness and ownership of the medication regimen.

Polypharmacy. Practice guidelines recommend adequate trials of single medications before the addition of a second, but real-world practice differs (3). Medicaid claims data have shown that psychotropic polypharmacy has risen consistently over the past two decades in various states (4,5). Although certain combinations of psychotropics have been shown to be beneficial in "treatment resistant" psychiatric disorders, the stability of the treatment-resistant label over time is unknown. In fact, Stahl and Grady (6) found in their review that most practitioners do not try to discontinue one of the drugs after a combination proves beneficial, even though such discontinuation would establish the true need for the combination. Meanwhile, the risks, especially with increasing age and general medical comorbidities, render the risk-benefit ratio even more disproportionate.

Implementing Deprescribing in Psychiatry

It is imperative that every psychiatrist be able to provide an individualized risk-benefit analysis of each medication for a given patient at a given time point, keeping in mind general medical comorbidities and psychosocial circumstances. Woodward (7) proposed the following five principles of deprescribing in geriatric medicine: review all current medications, identify medications to be targeted for reduction or cessation, plan a deprescribing regimen, plan in partnership with patients and caregivers, and provide frequent review and support. A review of more than ten studies of deprescribing found concordance in these five principles as the crucial elements of the process (8).

Further key considerations for psychiatry may be the timing and context of the change, the patient's alternative coping strategies, the meaning of the change for the patient, the strength of the treatment alliance, the level of risk, and whether the patient is receiving mandated treatment (see box). Environmental factors that could trigger relapse, including changes in housing, employment, finances, significant relationships, and even season, may need to be considered, along with holidays and anniversaries, in decisions about the timing of a deprescribing intervention. Furthermore, because risk behaviors vary widely among patients, the level of risk should be carefully considered in evaluating a patient for deprescribing. Accordingly, for patients with a history of suicide or homicide attempts, multiple hospitalizations in the recent past, severe relapses after dose reduction, or poor social support, deprescribing should be considered more cautiously (9). In all cases, one would also need to consider whether the patient is under mandated treatment and any expressed wish by the patient to reduce or discontinue medication.

Obtaining a complete list of the patient's medications and discussing the perceived risks and benefits of each medication should be the next step. As noted in geriatric medicine (10), barriers to obtaining a complete medication list include fragmentation of care and a failure to communicate the treatment rationale to the patient. Coordination with the patient's primary care physician may involve frequent oral communication and sharing of medical records. In generating a priority list of medications to consider for deprescribing, it is essential to ensure that all stakeholders are apprised of the evidence in regard to the risks and benefits of a medication. A medication with a high potential risk and low potential benefit would typically top the priority list. However, with psychotropic medications, we may encounter instances when the ratio is skewed in a particular direction because of a very high or low potential risk or benefit. For instance, although the risk of continuing benztropine in combination with haloperidol for five years might be considered low, the potential benefit is also low (perhaps lower than the risk for a given patient). For patients with multiple general medical comorbidities, a pharmacist's input on drug interactions and drug prescribing cascades might be invaluable.

Once the medication and tapering have been planned, the decision needs to be discussed with the patient's treatment team, including visiting nurses, social workers, case managers, and therapists. The patient's family, if involved, may be a valuable support for the patient. Patients may internalize anxiety experienced by their care providers, and this in itself could trigger psychological symptoms (11). Buy-in by family members and other care providers is therefore crucial, not only to minimize this effect but also to ensure early identification of relapse and avert hospitalization. The prescriber should also consider an additional risk—namely, the patient may interpret the proposal to deprescribe as a message that no treatment is warranted. Before the initiation of a taper, it may be worthwhile to spend several visits exploring the potential meaning of the change and developing an action plan in case symptoms recur and to manage withdrawal symptoms. The plan might include several nonpharmacological measures, such as increasing the frequency of visits to a therapist, developing a Wellness Recovery Action Plan (12), connecting with peer support, and teaching the patient and caregivers to identify early warning signs of illness relapse.

Deprescribing psychotropic medications[a]

Step 1: Choose the right time

- Avoid times of crisis or acute phase of illness
- Ensure that the treatment alliance is well established
- Use caution when the patient is actively abusing substances

Step 2: Compile a list of all the patient's medications

- Document dose, route, expected duration, and original indication
- Document current therapeutic and adverse effects
- Estimate potential drug-drug interactions and future risk-benefit ratio

Step 3: Initiate the discussion with the patient

- What is the patient's knowledge and attitudes about the medications?
- What is the patient's perception regarding the benefits and risks of each?
- Explore the meaning of medication(s) to the patient

Step 4: Introduce deprescribing to the patient

- Inform the patient about potential indications for and the process of deprescribing
- Solicit ideas, concerns, and expectations
- Address any anxieties on the part of the prescriber, patient, family, or clinical care team
- Get family and caregiver buy-in

Step 5: Identify which medication would be most appropriate for a taper

- Collaboratively weigh pros and cons of deprescribing each medication
- Solicit the patient's preferences

Step 6: Develop a plan

- Set a start date and rate of taper
- Is a switch to another medication or formulation indicated?
- Reinforce alternative biopsychosocial strategies for addressing symptoms
- Inform the patient about expected and possible discontinuation effects and their timing
- Agree on a monitoring and follow-up schedule and crisis plan

Step 7: Monitor and adapt, if necessary

- Adjust rate of taper
- Treat discontinuation syndrome or relapse
- Abort or defer deprescribing

[a] Although the entire array of medications taken by a patient needs to be considered for deprescribing, psychiatrists may focus on psychotropic medications and provide the impetus for deprescribing of other medications through coordination with primary care physicians and pharmacists.

Symptoms of withdrawal from antidepressants, antipsychotics, and anticholinergic agents have been well described in the literature. In psychotic disorders, delineating withdrawal psychoses from a true relapse may be challenging. Similarly, in depressive disorders, many symptoms of withdrawal from selective serotonin reuptake inhibitors can be misinterpreted as symptoms of a depressive relapse. As with standard practice in prescribing a new medication, frequent visits during tapering of a medication are advisable. The rate of taper may need to be adjusted depending on the patient's experience, withdrawal symptoms, recurrence of symptoms, and interim stressors.

Potential Challenges

Arguably, the manner in which a medication is prescribed will determine the ease with which it may be deprescribed, if appropriate. As medication visits become briefer, the focus can potentially shift towards symptoms rather than a deeper, holistic exploration of the illness, which may breed superficial prescribing (that is, transactions of symptom and medication).

Many factors can contribute to anxiety about and resistance toward reducing or discontinuing a psychotropic medication for the psychiatrist, family members, and the patient, including a belief that mental illnesses require lifelong medication treatment

and distress related to both signs and symptoms. The prescriber may desire to maintain the status quo once stability has been achieved and may be reluctant to change medications. Furthermore, many long-term side effects are not immediately visible (for example, renal impairment) and may not be accompanied by subjective distress (for example, tardive dyskinesia), and the prescriber may not ask about certain side effects at every visit (for example, sexual side effects). It is not surprising that there is a wealth of clinical evidence for initiating psychiatric medications and little evidence for discontinuing them. Even if psychiatrists wish to deprescribe, the lack of guidelines and data on discontinuation of medications serves as a barrier.

Future Directions

As in the study by Farrell and colleagues (13), discussion by a panel of psychiatrists, primary care physicians, pharmacists, social workers, therapists, and patients may help formulate a consensus hierarchy of medications for deprescribing in psychiatry. Within individual systems of care, multidisciplinary "deprescribing committees" could be modeled on a traditional consultation service. The committees could prepare a report for patients and prescribers that includes a hierarchy of medications that could be reduced or discontinued and a plan to manage emerging issues. It will be essential to develop strategies for closer coordination with primary care physicians so as to implement deprescribing as a general medical strategy (including all the medications that a patient takes) rather than restricting it to psychiatric medications.

Introducing the concept of deprescribing in psychiatric training and generating guidelines based on existing literature are important first steps. Although discontinuation trials exist in psychiatry, further research is indicated to refine the parameters of "good deprescribing" in the biological, psychological, and social domains. Rossello and colleagues (2) have called for a reexamination of long-term prescriptions of many cardiovascular drugs. Similarly, existing data on long-term medication management in psychiatric disorders may need to be reexamined critically with a view to identifying patients for whom deprescribing might be successful. Studies of receptor changes and their correlation with withdrawal symptoms could provide useful data on managing and preventing withdrawal syndromes. The Patient Attitudes Towards Deprescribing Questionnaire (14) has been used in geriatric medicine and could be adapted for psychiatry to measure the acceptability of deprescribing.

Conclusions

In response to a growing awareness of adverse medication effects, the impacts of patients' changing physiology and psychosocial context, and the benefits of patient-centered practice, the intervention of deprescribing has much to offer psychiatry. For patients who choose to manage their psychiatric illness with fewer or no medications, psychiatrists must be equipped to collaborate in analyzing potential risks and benefits and developing a plan for managing withdrawal symptoms and relapses. Critical review of the existing literature and new research on deprescribing interventions in psychiatry are needed.

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WORK 7

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EMPIRICAL REPORT

Psychopharmacology Prescribing Workshops: A Novel Method for Teaching Psychiatry Residents How to Talk to Patients About Medications

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Abstract
Objective Traditional, lecture-based methods of teaching pharmacology may not translate into the skills needed to communicate effectively with patients about medications. In response, the authors developed an interactive course for third-year psychiatry residents to reinforce prescribing skills.
Methods Residents participate in a facilitated group discussion combined with a role-play exercise where they mock-prescribe medication to their peers. Each session is focused on one medication or class of medications with an emphasis on various aspects of informed consent (such as describing the indication, dosing, expected benefits, potential side effects, and necessary work-up and follow up). In the process of implementing the course at a second site, the original format was modified to include self-assessment measures and video examples of experienced faculty members prescribing to a simulated patient.
Results The course was initially developed at one site and has since been disseminated to a number of other institutions. Between 2010 and 2016, 144 residents participated in the course at the authors' two institutions. Based upon pre/post surveys conducted with a subset of residents, the course significantly improved comfort with various aspects of prescribing. Although residents may also gain comfort in prescribing with experience (as the course coincides with the major outpatient clinical training year), improvement in comfort-level was also noted for medications that residents had relatively little experience initiating. At the end of the year, half of the residents indicated the course was one of their top three preferred methods for learning psychopharmacology in addition to direct clinical experience and supervision (with none listing didactics).
Conclusion An interactive prescribing workshop can improve resident comfort with prescribing and may be preferred over a traditional, lecture-based approach. The course may be particularly helpful for those medications that are less commonly used. Based upon our experience, this approach can be easily implemented across institutions..

Keywords Residents · Psychopharmacology · Teaching methods

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There is no consensus about the best way to teach psychopharmacology to psychiatry residents. Historically, psychopharmacology has been taught in a passive way with residents attending lectures where each class of medication is reviewed [1, 2]. Residents are often presented with a large amount of information about each medication and are faced with the challenge of integrating multiple resources, including expert guidelines and clinical trials [3]. Expecting residents to memorize the amount of material presented to them during these lectures is unrealistic. It is also not clear how well this approach translates into the actual skills required to prescribe these medications to patients [2].

The act of good prescribing requires more than acquired knowledge—psychiatrists must draw upon a combination of communication skills, ethics, therapeutic process, and professional identity. Residents need to be able to present material clearly and obtain informed consent, all while remaining attuned to psychological factors within the doctor-patient

relationship that plays a role in medication response [4, 5]. Translating knowledge about medications in a way that is easy for patients to understand is not a skill that is usually taught in a classroom. For example, residents may learn in a classroom that lamotrigine has a rare but serious side effect of Stevens-Johnson Syndrome, but may not know how to discuss this risk with a patient without generating excessive anxiety.

These skills are also challenging to teach in modern treatment settings. The "see-one, do-one, teach one" model of adult learning assumes these types of conversations are modeled by supervisors and that residents have clinical experience with all of the medications that have been discussed in the classroom. However, this is frequently not the case. Training in psychopharmacology is often highly variable, depending on the expertise of the faculty supervisor and the unique caseload of patients that each resident sees. In treating individual patients, residents often have guidance in terms of medication choice and dosage but not necessarily explicit advice about how to talk to patients, especially during their Postgraduate Year 3 (PGY3) where direct supervision in outpatient care is limited [6]. In addition, not every supervisor emphasizes how these conversations might be customized to address individual factors unique to the patient but highly relevant to treatment decisions [4, 7]. Furthermore, residents may get considerable experience using first line agents (such as a selective serotonin reuptake inhibitor, or SSRI, for depression) but may not get any practice prescribing third line agents (such as a monoamine oxidase inhibitor, or MAOI), further limiting their clinical educational experience.

To address these gaps in the clinical experience, psychopharmacology curricula in residency have started to include more interactive options. While these strategies (such as problem-based learning and interactive games) have been well received and cover basic facts about medications in an interactive manner, they do not address the question of what the physician actually says to patients about medications [8, 9].

At the same time, the milestones initiative within residency training requires programs to perform more objective assessments of residents' patient care, medical knowledge, and communication skills [10]. The ability to communicate clearly and discuss treatment options with patients cuts across all of these domains and is an important skill set to assess during residency training.

Here, we present the development, adaptation, and evaluation of a prescribing workshop course that reinforces acquisition of medical knowledge related to psychopharmacology and addresses the communication skills needed to effectively prescribe medications. Our goal was to create a new framework for teaching psychopharmacology that gives residents prescribing experience in a structured classroom setting and to provide a model for teaching psychopharmacology that translates directly to clinical practice. We hoped the interactive format of this course would be engaging for residents and would improve resident comfort with the various elements that go into prescribing. These include discussing with patients; recommended treatment options; how to take specific medications; benefits and potential limitations (including adverse effects); mechanisms of action; relevant work up; and other considerations.

Course Development

The course was developed for third year (PGY3) psychiatry residents. We felt PGY3 residents were an appropriate audience for this course as they are transitioning to a more autonomous role in the outpatient setting, often without direct supervision. Therefore, their motivation to learn the various skills of prescribing in the outpatient setting is very high.

The organizing principle of the course was straightforward: we want to ensure that residents will be safe and effective prescribers of psychotropic medications. To this end, we designed a course frame that focuses on this explicit behavioral skill: each session centers on a resident having the opportunity to role play prescribing a medication in a safe setting and with the opportunity for structured feedback. Each "prescriber's workshop" is devoted to a designated medication class or clinical concept (such as augmenting agents). Residents are expected to prepare basic information about the specified medication before each session in a flipped classroom model using a standard template and be ready to apply this basic information to a clinical scenario. (A copy of the template is available upon request.)

Structure of the Yale Workshop

The original workshop developed at Yale in 2010 is a 75-min workshop with approximately 20 sessions over the first 6 months of the PGY3 year. Each session is divided into three equal parts designed to address knowledge, skills, and process. The first 15–20 min of each workshop is a review of the information entered into the template to consolidate knowledge, allow for questions, and ensure that each resident is comfortable with the core content. The next 30 min of the workshop is devoted to a role-play exercise. During this section, residents break up into groups of three: one resident plays the role of prescriber, another plays the role of the patient, and the third acts as observer (faculty members also circulate to offer additional feedback). Following the encounter, the small group has time to discuss the role play. The residents then rotate so that each resident has an opportunity to play each role. For some sessions, faculty demonstrates an example of what they might say to a patient while prescribing the assigned medication. The final 25 min of each workshop is designated for group reflection and discussion of the processes that

occurred during the role-play (such as things that worked well or were more challenging).

Several challenges arose after the start of this course. In the first year of the workshop, different expert psychopharmacologists taught individual sessions, each on the area of his or her expertise. This led to variability in class frame, with some sessions deviating from the intended structure. At the beginning of the course, the initial review of medication facts at times devolved into discussions of esoteric details rather than practical prescribing information. Furthermore, role-play exercises were initially limited by mutual anxiety: residents would be anxious to prescribe a medication in front of peers and supervisors; expert faculty—often participating in one or two sessions only—at times felt uncomfortable engaging in a teaching format with which they had no experience. As a result, residents and faculty could together collude to avoid the role-play exercise.

To address these challenges, two faculty members were recruited in the second year to co-direct the course. One faculty member had relative strength for general psychopharmacology knowledge and the other had relative expertise in therapeutic communication and in managing group process. Having the same two individuals run all sessions dramatically enhanced group comfort with the exercise and ensured consistency in the workshop frame throughout the course.

Adaptations at Columbia

Using the general framework developed at Yale, Columbia decided to implement a similar course for PGY3 residents starting in 2013. The course started out as a year-long monthly 60-min workshop and was expanded during the second year of implementation to twice a month for 75 min each. Adaptations included (1) addition of an educational videoseries demonstrating how a panel of expert psychopharmacologists discuss various medications with patients; (2) the inclusion of additional preceptors (faculty and PGY4 volunteers, instead of peers) to observe, assess, and provide feedback for residents working in pairs; and (3) administration of pre and post workshop self-assessments measuring resident comfort level in the different tasks of prescribing.

In order to build in time for the expert videos and the discussions that follow, there is no review of the medication information template in class. Each workshop begins with the presentation of a brief clinical scenario (e.g., "Patient is a 24-year-old man presenting with his first major depressive episode, you will now discuss starting citalopram"). Participants then divide into groups of three consisting of two PGY3 residents and one preceptor (either a faculty member or a PGY4 resident volunteer). Following each role-play, preceptors help to facilitate discussion and provide feedback.

Educational Videos Since PGY3 residents almost never observe experienced psychopharmacologists start medications with outpatients, we felt it would be educational for residents to have a chance to see how experienced faculty members discuss medications with their patients. Residents tend to feel more confident when they have one-to-one supervision with a senior clinician, and videotapes are a method for making this experience accessible to more residents (especially considering the time constraints faced by senior clinicians). A library of videos was created of expert psychopharmacologists role-playing how they talk to patients about specific medications. As an example of content, one video is of a psychopharmacologist who specializes in affective disorders prescribing lithium to a fictionalized patient. In addition to the demonstration, these videos often include "clinical pearls" at the end.

The video corresponding to the designated medication was played at the end of each workshop so residents could observe a particular prescribing style *after* they all had a chance to complete the role-play exercise. This was meant to encourage residents to think through the material themselves and not feel as though there is only one correct way to discuss a medication with a patient.

Course Preceptors There is a core group of faculty and PGY4 preceptors with up to four present at each workshop (in addition to the course directors: a psychopharmcology expert and the director of the outpatient clinic) to observe the role-plays. The goal of involving PGY4 residents as preceptors was that they would help PGY3 residents feel comfortable while demonstrating the remarkable growth in knowledge and skill the residents will acquire by the end of their third year. Of note, many PGY4 residents have volunteered to participate as it gives them an opportunity to teach and consolidate their own learning. Preceptors and faculty were provided with checklists of elements of prescribing to guide their listening and discussion during the role-play exercise and to remind them of teaching points.

Course Assessments At Columbia, self-assessment tools were added to see whether the goals of learning were met. The Institutional Review Board (IRB) of the New York State's Psychiatric Institute determined that this study was not human subject's research and was therefore not subject to IRB review. Residents were surveyed in two ways: 1) pre and post surveys within each workshop focusing on the comfort level discussing various factors of a specific medication with patients, to measure the impact of the class itself and 2) pre and post course surveys about actual clinical experiences and comfort with prescribing various medications, to measure the impact of the course as a whole versus other methods of teaching psychopharmacology

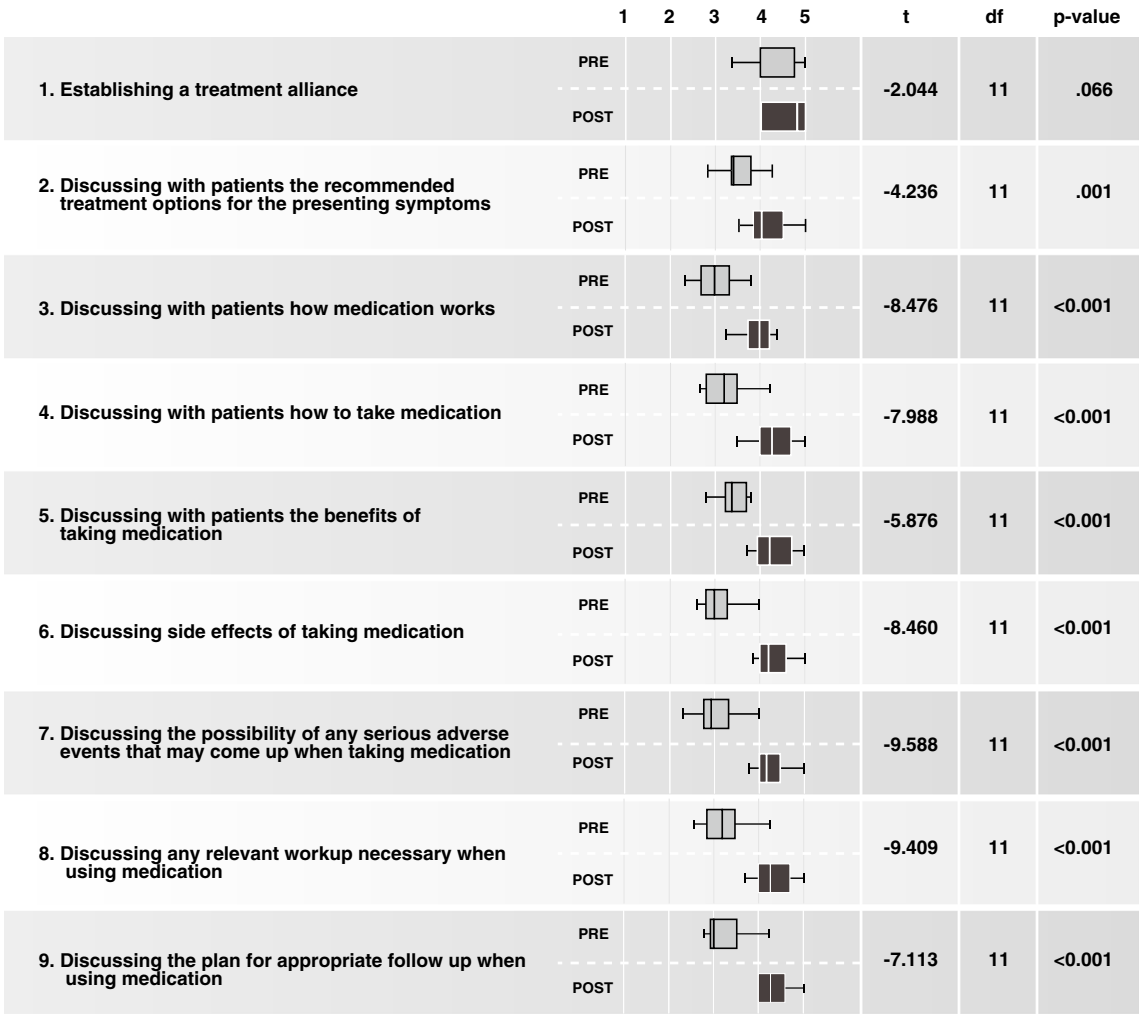

Fig. 1 *Boxplots* of pre–post workshop assessments for each of the nine comfort questions with individual paired *t* tests. *Vertical lines* represent the mean, with the surrounding *box* representing the 25th and 75th percentiles and the *whiskers* representing the 5th and 95th percentiles

(i.e., direct supervision, online resources, traditional didactics). Both types of surveys used a 5-point Likert-type scale. Individual workshop data was collected and analyzed for participants at Columbia during the inaugural year of the course in 2013–2014. Data were collected before and after individual workshops on SSRIs, MAOIs, tricyclic antidepressants (TCAs), stimulants, valproic acid, lithium, and lamotrigine. Outcome data were analyzed using a paired *t* test of pre and post assessments.

Since this course coincided with the residents' major outpatient clinical year, we sought to understand the potential value of the course while taking into account the fact that our main outcome (comfort level in prescribing) would likely increase based upon experience alone (which included weekly supervision in psychopharmacology and experience prescribing medications in managing outpatient caseloads). Based upon one of the original goals of the course, we hypothesized that the course would be particularly beneficial for learning how to prescribe those medications that were less commonly used in clinical practice. For each medication (or medication class), we calculated the percentage of residents who reported initiating treatment more than two times by the end of the year. We specifically focused on resident experience of *initiating* treatment (as opposed to prescription renewal) since this was the focus of the workshop. We then looked at gains in comfort level across medications taught in the course that were commonly initiated by residents in comparison to those that were not commonly initiated. As a control, we also assessed resident comfort level in initially prescribing medications that were not commonly used nor taught in prescribing workshop course.

Results

Between 2010 and 2016, 144 psychiatry residents have participated in the prescribing workshop across both

Table 1 Resident comfort level with initiating treatment for various medications (or classes of medications) at the beginning and end of the year-long course based upon a 5-point Likert-type scale

Medication	Percentage with substantial experience* ($n = 11$)	Pre mean	Pre SD	Post mean	Post SD	Corresponding workshop	Paired t test (p value)**
Buprenorphine	0%	1.45	0.69	1.82	0.75	No	NS
Disulfiram	0%	1.55	0.69	2.00	0.63	No	NS
Clozapine	27%	2.27	0.79	3.09	0.94	No	NS
TCA	0%	2.09	0.54	3.64	0.92	Yes	0.001
Lamotrigine	18%	2.45	1.21	3.82	0.75	Yes	0.016
Stimulants	36%	2.18	0.75	3.82	0.60	Yes	0.000
Lithium	82%	2.82	0.98	4.09	0.94	Yes	0.014
Depakote	100%	2.91	1.04	4.18	0.60	Yes	0.008
SSRI	100%	4.09	1.04	4.82	0.60	Yes	NS
Atypical Antipsychotic	100%	3.64	1.21	4.36	0.67	Yes	NS

The Likert scale included the following anchors:

(1) Would not prescribe this medication on my own to a patient today

(2) Would not prescribe without having the opportunity to read/learn more before sitting with patient

(3) Would prescribe if necessary and might want to consult a resource before prescribing

(4) Likely would prescribe this medication on my own but might double check something afterwards

(5) Totally comfortable prescribing this medication and would do so without hesitation

*Substantial experience was defined as *initiating* treatment more than twice by the end of the outpatient clinical year

**Significance at the $p < .05$ level

institutions (108 from Yale and 36 from Columbia). In order to determine the overall impact of the course, data from each workshop at Columbia held between 2013 and 14 were combined and a paired t test was performed on pre/post assessments (58 total paired entries from 12 participating residents). As displayed in Fig. 1, residents reported significant improvement for every question assessing comfort, with the exception of the one focusing on "establishing a treatment alliance" which was relatively high at baseline.

In the inaugural year of the workshop at Columbia, 11 participants also completed assessments at the beginning and end of the year. As shown in Table 1, more than 50% of residents reported relatively limited experience in prescribing a subset of medications (e.g., TCAs, lamotrigine, and stimulants). Despite this limited experience, residents showed sustained significant improvement in comfort prescribing these medications at the end of the year ($p < .05$). As a comparison, for less commonly prescribed medications where there was no corresponding workshop (e.g., disulfiram, buprenorphine, clozapine), residents did not show significant improvement over the course of the year in terms of comfort prescribing. For more commonly prescribed medications for which there was also a workshop (e.g., SSRIs and second generation antipsychotics), there was no significant improvement in comfort over the course of the year and the initial comfort in prescribing these medications at the beginning of the year started at a higher baseline (>3.5). For commonly prescribed medications where initial comfort started at a baseline of <3 (e.g., valproic acid and lithium), there was still a significant improvement in comfort after the year ($p < .05$), though it is unclear if this is related to this course or clinical experience.

Residents in the first year of the workshop were asked to list their top three preferred methods for learning psychopharmacology during their PGY3 year. While none of the residents listed traditional didactics, 50% of residents indicated that the prescriber workshop was one of their preferred methods of learning. All residents listed clinical experience as their number one method for learning psychopharmacology.

Discussion

These data support the value of a prescriber's workshop for improving resident comfort with various aspects of prescribing and suggest that residents see the course as a useful method for learning psychopharmacology. The data also indicate that residents prefer this workshop-format over a traditional, lecture-based approach. The pre- and post-course data collected in the first year at Columbia suggests that this course can lead to significant improvement in

comfort with prescribing medications even with little to no corresponding clinical experience, which may help residents feel more comfortable in considering these medications as treatment options for their patients in the future. This is especially encouraging in that an original goal of the course was to address a frequent complaint of graduating residents that they never prescribed certain rare medications (e.g., an MAOi or TCA)—following this course, residents will have prescribed all of these agents at least once with supervision (albeit in a mock setting).

These workshops do not significantly improve residents' comfort with establishing a treatment alliance, which is not surprising as baseline comfort level was reported to be high. This is likely because building an alliance is a skill that is emphasized in all areas of clinical care during residency, including psychotherapy training, and is usually taught much earlier.

Limitations of this study include the fact that although there were a large number of participants across both sites, the subset of residents who completed assessments is relatively small. Furthermore, while these assessments focused on resident comfort with prescribing before and after each workshop, we did not assess actual prescribing practices after the completion of the course.

Despite these limitations, the course has consistently received positive feedback across both institutions. At Columbia, 10 out of 24 participants in the first 2 years of the course have returned to serve as preceptors during their PGY4 year, which may have helped to provide them with repeat exposure to this intervention and consolidate gains. The addition of a library of videos of psychopharmacology experts not only addresses the challenge of limited time and access to expert psychopharmacologists but also makes the workshops easier to implement. Because of these videos, the faculty and PGY4 preceptors present during the workshop do not need to be experts in the assigned medication being discussed. Both versions of the course have been implemented at other programs and have received consistently positive feedback. The Columbia group is working to make their videotapes available through a protected residency-wide wiki page so that residents can access them after the course (particularly for those they miss) and, ideally, so that they can ultimately be made accessible to other academic institutions for training purposes.

Teaching psychopharmacology in residency has historically been challenging, as the act of prescribing draws upon many factors and depends upon the integration of many sources of information. Using an interactive practice-based approach can help residents master not only the details of medications, but also how to think critically to present the material to patients clearly and improve their comfort as prescribers. It is encouraging that these skills, traditionally felt to be gained only through clinical experience, can be strengthened in a formal and standardized classroom setting.

Compliance with Ethical Standards

Disclosures On behalf of all authors, the corresponding author states that there is no conflict of interest.

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REVIEW ARTICLE

Building Early Intervention Services for Psychotic Disorders: A Primer for Early Adopters in the U.S.

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Abstract: Recent developments in the U.S. healthcare policy signal a growing commitment to early intervention for psychotic disorders. A growing international and U.S. research database supports the effectiveness of specialty team-based models adapted to care for young individuals with recent onset psychosis. The RAISE (Recovery After an Initial Schizophrenia Episode) initiative, sponsored by the NIMH (National Institute of Mental Health), has defined such Coordinated Specialty Care (CSC) services as a new benchmark for care across the U.S., and published a variety of resources to support dissemination. Funding initiatives led by the center for Substance Abuse and Mental Health Services (SAMHSA), and support from other national organizations, have catalyzed interest in community agencies across the country. We offer guidance to such early adopters and supplement extant resources with a focus on the process of setting up such programs. Adopters have numerous decisions to make. These include determining admission criteria, structuring care processes to maximize impact, choosing from several empirically based interventions, and resourcing workforce development. We provide a guide to salient resources, and lessons learned from a decade old CSC, to aid in these complex decisions. We end with a discussion of limitations in the current knowledge base, and the need for responsive research. Early intervention services can engender application of demonstrably effective treatment, while also providing platforms for research to improve and develop new treatments. Collaborations between a wide variety of government, academic and commercial stakeholders will be essential to realize the transformative public health impact of early intervention for psychotic disorders.

Keywords: Psychosis, early intervention, first episode, schizophrenia, coordinated specialty care.

1. INTRODUCTION

The U.S. may be in the midst of a transformation in the delivery of services to individuals and families confronting the recent onset of a psychotic illness. While the intuitive notion of early intervention is likely at least as old as the recognition of these disorders, the past two decades have seen this idea made operational in effective service models across several countries. Several pragmatic randomized trials of comprehensive team based care have been accompanied by national policies supporting systematic implementation [1]. Until recently however, the reality for patients in the U.S. has presented a paradox: while seminal research has emerged from this country, few systematic efforts had been mounted to disseminate services that can deliver empirically based interventions. In 2015, the publication of the first U.S. randomized trial demonstrated the effectiveness of a real-world public sector based service in Connecticut [2]; this was followed by a large cluster randomized trial demonstrating feasibility in community sites across 21 states [3]. This actionable evidence generated with funding from the National Institute of Mental Health (NIMH) has been accompanied by federal funding initiatives. The Substance Abuse and Mental Health Services Administration (SAMHSA) beginning in 2014, has directed that at least 10% of its Mental Health Block Grant (MHBG) to State Mental Health Agencies (SMHA), be dedicated toward early intervention services. As we have argued previously [4], SMHAs are a *de facto* national public mental health system, and have a strong incentive to invest in approaches to reduce the long-term morbidity of psychotic illnesses. The growth of new early intervention services across the U.S., in both public and private settings, spurred in part by this federal initiative, is a welcome development. This paper is targeted at such 'early adopters' in the U.S.

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2. BUILDING AN EARLY INTERVENTION SERVICE IN THE U.S.: WHERE TO BEGIN?

A map is not the territory ...

— Alfred Korzybski (1933, p. 58) [5]

Unlike previous pioneers in Australia, Canada, Northern Europe and the U.K., developers of new services in the U.S. can draw from a rich array of resources. Aside from informative reviews of international implementations [6], the RAISE project has assembled a vast online portal to support implementation of what the NIMH has usefully termed Coordinated Specialty Care (CSC). This label applies to a variety of services that share a comprehensive team based approach for new onset psychosis [7]. The web site includes links to empirical papers, manuals and webinars addressing a broad range of critical issues. Program developers can thus find detailed and essential 'maps' to guide their journey through the fragmented U.S. healthcare system. CSC based services can play a critical role in integrating local networks of healthcare providers towards the complex needs of these patients and their families. In keeping with the spirit of the epigraph, however, these maps cannot be expected to address all - or even the most salient - challenges that will arise for such early adopters. Also, while highlighting multiple destinations (e.g. infrastructure needs, workforce development, funding models, specific treatments), these maps can be intimidating to planners new to the needs of this population.

In what follows, we emphasize selected aspects of the work of a CSC, drawing from the evolving experiences of a decade old service (Specialized Treatment Early in Psychosis; STEP) [4], that can help guide the difficult decisions involved in setting up new services. This is intended to supplement, not replace the resources above, and far from being prescriptive, aims to clarify the many reasonable choices developers can make in the face of complex decisions. Perhaps more nebulous, but important, is our aim to elucidate a culture [8] of practice wherein the *espoused* values of early intervention are most likely to be actually *experienced* by patients, families, referrers and others in the community who have a stake in the health of emerging adults with new onset psychotic disorders.

2.1. Outreach: Acknowledging Local Pathways to Care

New programs might organize their thinking around the sequence of events in a putative pathway to care. Much has usually transpired before a patient becomes visible to most clinics, and developers might draw on their knowledge and experiences of local pathways to better curate entry into their services. Some CSCs use separate outreach teams who screen and evaluate patients at the point of referral and, if appropriate, connect them to the ongoing treatment team. Other clinics assign a clinician to be designated as the outreach and engagement coordinator. In either case, staff might endeavor an assertive, yet flexible, stance toward patients who may be reluctant because of prior aversive treatment experiences. Others may lack insight, suffer disorganization, or be otherwise unwilling to seek treatment despite concern from others. Critically important to the "front door" of a CSC is its network of referral sources: mental health professionals, schools and universities, law enforcement and other emergency personnel, youth organizations, members of the clergy, and community leaders. Ideally, these community stakeholders are familiar with the CSC team, the importance of early identification and referral, and will facilitate engagement. Fledgling CSCs would do well to invest in relationships with key members of these local networks, make the referral process as simple and rapid as possible, and provide education and consultation to ensure patients will be directed to CSCs in a timely and effective manner.

2.2. Screening: Admission Criteria

Patients' first contact with STEP begins with screening for program eligibility (see Table **1** for our current criteria). Programs can use conceptual and pragmatic considerations to develop their own criteria. Barriers, such as the divide that exists in some states between separate systems that serve those under and over age18, or with private or public health insurance, or residence in certain catchment areas, may need to be addressed [4]. In addition to catchment area restrictions that may exist within their organization, implementers should consider travel time and what they consider a safe distance for managing clinical crises if they plan to offer mobile or home based services, as well as population size needed to recruit a sample large enough to justify a specialty clinic while maintaining reasonable staff:client ratios and a strong referral network. Depending on program priorities and clinical capacity, implementers will need to define the target sample, and can draw on various, defensible precedents [9]. Some combination of time since illness onset (e.g. within the first 3-5 years since frank psychosis) and age range (e.g. 16-35yo) will help delimit a population around which to organize a coherent, developmentally appropriate model of care. While programs may wish to target their services to those in the earliest stages of psychosis or have patients within a narrower phase of development, criteria that are too restrictive may confuse referrers and delay access. Most early intervention programs around the world have focused on the treatment of primary psychotic disorders, and though co-morbidities are expected, primary affective disorders;

Table 1. STEP inclusion and exclusion criteria.

Domain	STEP's Criteria
Age	16-35 y.o.
Diagnoses	Excluded for: Psychosis confirmed to be secondary to substance use or a medical condition; Bipolar or depressive disorder with psychotic features; Autism spectrum disorder with new onset psychosis.
Estimated illness duration	≤3 year since onset of psychosis
Treatment history	No exclusions for past treatment
Insurance status	No exclusions
Town of Residence	10 surrounding towns
Estimated Cognitive Ability	Exclude for IQ below 70 or eligibility for State DDS

substance-induced psychosis; psychoses secondary to some medical conditions; autistic spectrum disorders and severe intellectual disabilities are examples of disorders for which patients may be better served elsewhere. Regardless of which criteria are selected, the screening process should allow for prompt determination of eligibility so as not to contribute to referrer burden, delay access, or complicate pathways to care. There is considerable ambiguity in early presentations of these illnesses, and programs will have to determine to what degree they will err on the side of inclusion versus exclusion. For example, a policy of including individuals with a high suspicion of Bipolar Disorder that is only confirmed on follow-up will require that the service be able to care for a wider range of pathology, but will protect it from inappropriate exclusion of primary psychotic illnesses that present with affective symptoms.

2.3. Diagnostic Evaluation

CSC services are designed to assertively engage and treat primary psychotic disorders in the phase of emerging adulthood. Although recognizable by characteristic syndromal presentations and longitudinal course, these are diagnoses of exclusion. A multitude of medical conditions and drug-induced states can mimic primary psychoses. Patients with psychotic symptoms that are secondary to an identifiable cause often require distinct treatment and referral away from a CSC. Professionals working in a CSC may be the first to conduct a diagnostic assessment for rare secondary causes [10]. Careful history taking, physical and laboratory examination, targeted follow-up for unusual presentations or treatment resistance and continued vigilance for the emergence of signs or symptoms suggestive of 'medical mimics' of primary psychotic disorders can reduce the risk of misdiagnosis. After careful exclusion of secondary causes, considerable ambiguity is to be expected in classifying early-course primary psychosis. For example, the variability in expression of symptoms and lack of an extended or reliable longitudinal history in young patients can make it difficult to distinguish between depressive or bipolar disorder with psychotic features and schizophrenia spectrum disorders. It is helpful to avoid premature closure on a diagnosis and to encourage patients and their families to exercise the same caution while focusing on symptom control, rehabilitation of functional disabilities, and continued longitudinal evaluation.

2.4. Engagement Into Care

Inability or unwillingness to acknowledge having a serious mental illness is a common challenge to effective engagement. Patients may be reluctant to agree that treatment is important but will often readily identify the need for assistance in getting a job, going to school, improving social relationships, or improving difficulties with thinking. A responsive 'menu' of interventions that includes structured supports for finding employment or resuming high school, college or vocational training and approaches to improve social skills and cognition can help improve engagement [11] and offers the possibility of mutually reinforcing effects on functional outcomes.

Just as important as *what* is *how* services are offered. The culture and values of CSC teams are essential. It is important to maintain optimism, a focus on recovery toward personal goals, and a collaborative therapeutic alliance. Often, patients may not believe that they are in need of mental health treatment, thus making engagement one of the most critical elements of care. Patience and flexibility can help avert power struggles. It can be useful to connect with patients around their interests, understand what trajectory of wishes or plans were interrupted by the illness, [11] and explicitly recognize and value their goals, even when this might conflict with those of the family or treatment team. Clinicians should emphasize what the program or clinic can offer to match the patients' priorities and be prepared to address confusion, stigma, or pessimism about the causes or treatment of mental illness amongst patients, families or referrers. Flexibility whenever possible around length and scheduling of appointments is encouraged.

An initial detailed assessment can facilitate engagement by expanding the discussion beyond symptoms to include social and vocational goals that are often most important to patients, and communicating (verbally and nonverbally) comfort with discussing unusual or bizarre material. Patients may present with disorganization or agitation that clinicians would do well to respond to with patience and validation of what that experience is like rather than immediately debating the content or explanation of those experiences. Despite initial resistance and limited or absent insight, many patients respond well if given an opportunity to feel heard and if the clinician's perspective is only offered after careful assessment and, preferably, with the patient's permission.

Inclusion of family members and other naturalistic supports is an essential component of CSC. Families, in addition to their vital role in patients' lives, can provide invaluable historical information for diagnosis and treatment selection, collaborate in monitoring for safety, and report early warning signs of psychotic relapse. The emotional environment they provide the patient is one of the strongest predictors of psychiatric relapse and hospitalization. Enabling families to recognize and reduce high levels of "expressed emotion"—criticism, lack of warmth, hostility, and emotional over-involvement—is likely to have tremendous benefit. Families should be treated as allies and members of the treatment team. They may present with incorrect attributions regarding illness, be frightened by aggressive or disorganized behavior, need to grieve the loss of the future they had envisioned for their child, or express frustration at clinical staff after experiencing convoluted pathways through care. It is important to keep in mind that initial meetings with families may come at what is the worst time for them. Many may have recently had a frustrating experience seeking help for their ill relative. Empathic and patient responses to their initial requests can go a long way. Reassurance, education, and communication of optimism from the clinician are useful and appropriate.

2.5. Putting Together and Delivering a Package of Care

A broad menu of interventions will allow flexible matching and refinement to dynamic patient priorities. Implementers should start from within a range of empirically supported treatments used in CSCs around the world [6] or SAMHSA's Inventory and Environmental Scan of Evidence-Based Practices for Treating Persons in Early Stages of Serious Mental

Disorders [12], before mounting *de novo* approaches. Participation rates in group-based interventions in early-psychosis samples can be low, and given many patients will be attending work or school, attendance in all interventions offered within a CSC may not be realistic or desirable. Given limited resources, hard choices will need to be made on what to include in a package of care while keeping in mind that engagement and retention can be enhanced for this very heterogeneous population by offering a wider menu.

Many CSCs provide treatment in the community, similar to or following an Assertive Community Treatment (ACT) model of care. Patients are treated primarily in settings outside the clinician's office. Implementers of new CSC will need to determine what (if any) of their services can be resourced for delivery in the community and what crisis coverage will be available outside of usual clinic hours. For office-based services, an open access or partially open access model should be considered. Many patients, due to disorganization, reluctance or paranoia, have difficulty consistently attending scheduled appointments. In our CSC (STEP), we offer scheduled appointments later in the day but patients who are unable or unwilling to adhere to them are encouraged to "drop by anytime" early in the day. The team-based approach described below ensures that any of the CSC staff will be familiar enough with the patient to engage with them should their primary clinician not be available.

Consistent across CSCs is the use of interdisciplinary teams. Various disciplines bring diverse perspectives to understanding and treating patients that can be leveraged in a pluralistic model of care. This includes psychiatry, psychology, social work, nursing, occupational therapy, and persons with lived experience of a mental illness. Roles can be assigned based on aptitude and skill rather than merely along disciplinary lines. For example, any of the clinical disciplines can serve in the essential role of primary clinician (i.e. the point person who coordinates and tailors CSC care for their assigned patients). Alternative or additional roles for the same clinician can include education and support of the family or therapy for patients in an individual or group modality. However, the supported employment and education role requires significant time in the community to develop relationships with employers and areas colleges and to assist patients on site. This role is thus less likely to be inter-changeable among the clinicians. Psychiatrists or advanced practice nurses typically provide medication management, coordinate with primary care, and play a pivotal role in differential diagnosis, physical health monitoring and inter-vention. A designated team leader (again, drawn from any of the clinical disciplines) can coordinate clinic activities, lead team meetings, provide supervision, oversee development and implementation of services, ensure adherence to treatment philosophies, and even carry a caseload as primary clinician.

Weekly interdisciplinary team meetings and frequent communication ensure fidelity to treatment principles, facilitate morale, and encourage high-quality service delivery. Care should be taken not to fall into a pattern of focusing only on crises or negative outcomes in young patients, whose setbacks can be felt deeply by clinicians. Periodic signposting of meaningful improvements at a patient level (e.g. interviewing for a job or more consistently attending appointments) and population level (e.g. % employed or in school, % with positive symptom remission) can contextualize an inevitable focus in clinical meetings on the highest need patients. Periodic thorough case reviews can be used to illustrate values and practice ethos, troubleshoot treatment challenges and also effectively reveal training needs [13].

A practice these authors have found useful, is a daily morning 'huddle.' This is a brief daily meeting amongst the team leader and primary clinicians to triage new referrals, trouble-shoot emerging crises, coordinate simultaneous care to patients and families, and plan coverage for unforeseen staff absences.

While this may improve as CSCs become more prevalent, new programs will likely recruit staff without prior experience of this model of care. Training clinicians with structured treatment manuals can ensure that adequate background knowledge is communicated, even as defined skills are developed. Another important aspect of on-boarding many clinicians is to help them develop confidence in adapting their existing clinical skills to an early psychosis population. While specialized knowledge of early stage psychosis is valuable, techniques used in various CSC interventions are within the skill set of most experienced clinicians. Just as crucial as training on specific interventions is building a culture of practice. Ongoing supervision and continuing education can reinforce core values of flexibility, teamwork, optimism, respect for patients' rights and autonomy, and toleration of uncertainty and risk.

Work in a CSC is aided by knowledge of common problems encountered in early-course psychotic disorders but also a more general understanding of the developmental psychology of adolescence and young adulthood. Also relevant, depending on the population under care, is knowledge of the impact of immigration and trauma or the interacting co-morbidities of substance use, suicidality, anxiety, and obsessive compulsive disorder (OCD). Patients and their families will likely have questions regarding substance use and its relationship to psychosis risk; providers would do well to become familiar with the literature on cannabis use in particular. Substance use in recent onset psychosis is associated with higher rates of relapse, poorer social functioning, and more severe psychopathology [14, 15].

In addition to elevated rates of trauma and stressful life events among recent onset psychosis populations, the experience of becoming psychotic is often frightening. Entry into treatment can involve aversive experiences including interactions with police, physical restraint, and involuntary hospitalizations. Assessing for and attempting to alleviate fears about treatment through reassurance, education, and a patient, therapeutic stance is essential. For example, a patient may be reluctant to engage and particularly guarded due to anxiety regarding involuntary hospitalization, but may be forthcoming if the criteria for emergency commitment are provided along with reassurance from the professional that this is a last resort. As always, careful consideration must be given when considering involuntary commitment.

Reducing immediate threats to physical safety (the patient's and others') while always a priority, must be managed with a view to long term, sustained reduction of this risk. The latter is threatened by the loss of the therapeutic alliance and departure from treatment. If hospitalization is necessary, clinicians can mitigate this risk of disengagement by effecting procedural justice for each patient (e.g., being treated fairly and respectfully, feeling heard, getting a chance to tell one's side of the story, being included in the decision process) and following up with the treatment team and patient during the ensuing hospitalization. As described earlier, engagement is a significant challenge in treating recent onset psychosis, and it is vital to proactively address fears or misunderstandings that can threaten a trusting therapeutic relationship.

Paranoia and persecutory delusions may also increase risk for aggressive behavior because patients may believe they are acting in self-defense. Although the majority of those in the early stages of psychosis will not be violent, they may still come into contact with the criminal justice system for illness related behaviors, such as trespassing or disorderly conduct. Professionals working within CSCs will likely find themselves interacting with the legal system regarding their patients. Understanding the local criminal justice system, as well as the ethical considerations of working with patients with legal charges or court-mandated treatment will prove useful.

Although positive symptoms often respond adequately to antipsychotic medication, the symptoms that can have the greatest impact on functional recovery—negative and cognitive symptoms—typically do not. Distinguishing and reducing the impact of depression, medication side effects or social isolation [16] can help many with negative symptoms, but research has yet to deliver effective treatments of any remaining deficit symptoms. Cognitive remediation programs have shown promise in reducing the intellectual deficits that typically develop in schizophrenia and, in combination with other approaches, like supported employment, might have particular promise in improving functional outcomes. Professionals working within CSC should familiarize themselves with the common cognitive symptoms associated with psychosis, such as executive functioning deficits, and consider referral for neuropsychological assessment. Such an assessment can evaluate the extent of dysfunction compared to population norms, monitor for changes over time, and suggest strategies to reduce their impact on school and work function.

Individuals with chronic psychotic disorders are well known to suffer premature mortality, mostly from cardio-vascular diseases. Key risk factors that emerge in early psychosis populations are obesity and smoking [17]. Positive and adverse health behaviors may be consolidated during early illness and predict long-term behavior. CSCs thus might have a window of opportunity to modify lifestyle habits that can have a pervasive impact well into adulthood [17]. Strategies to optimize cardiovascular health within a CSC can mirror the overall ethos of maintaining a patient-centered and flexible approach. Biological (e.g. antipsychotic induced weight gain, familial hyperlipidemia), psychological (e.g. maladaptive health beliefs, lack of education) and social (lack of access to healthy foods or gyms, family norms) factors, potentially contributing to cardiovascular health, must all be addressed. Many patients may be interacting with healthcare providers for the first time as adults. Others may come from a culture of seeking primary care *via* ad hoc emergency room visits only. Therefore patients must be empowered with education and resources, whilst potentially shifting attitudes towards health and healthcare. It may be developmentally unrealistic to expect younger patients to expend significant effort to avoid the cardiovascular morbidity of middle age and beyond. However, this can be tackled therapeutically in the same way as acceptance of illness, prognosis and chronicity of maintenance phase treatment. If a patient does not shop and cook for themselves, the involvement of the family may be necessary to address diet, portion sizes and access to healthy snacks.

The importance of cardiovascular health and monitoring for metabolic side effects of treatment should be addressed early in the course of care, not only to reduce long-term risk, but also to preserve and strengthen the treatment alliance as problems such as weight gain emerge. STEP's approach is to instigate a 'wellness visit' with a nurse within 2 weeks of admission. During this visit admission laboratory testing is reviewed or ordered for fasting glucose and lipids, electro-cardiogram, urine toxicology and pregnancy tests are obtained and vital signs and weight are recorded. Past medical history (and family history) is reviewed, paying particular attention to the client's diet and exercise practices and attitudes to health and wellness in order to identify potential areas of education and development. Counseling may be provided around contraception and seeking routine health surveillance *via* primary care or gynecology. If necessary, patients are engaged around a primary care referral; otherwise releases of information and records are obtained from other providers (if they have not been already). A monitoring schedule for those taking antipsychotic medications can be drawn from extant guidelines [18].

If smoking is identified, counseling is provided and motivation to quit is assessed within a motivational inter-viewing stance. If appropriate, goals for harm reduction or a quit date is set. Conventional therapeutic and medication strategies to support abstinence are offered. These may include motivational interviewing, cognitive behavioral therapy based groups, nicotine replacement therapy, bupropion and varenicline.

2.6. Evolution and Refinement of Services

Early adopters can assure themselves that though several decisions are necessary in the implementation and development of a CSC, few, if any, of these decisions should be considered final. Our package of care in STEP has changed in numerous ways over the course of our first decade, with interventions, strategies, and inclusion criteria being modified or replaced to better fit the needs of our patient population, resources, and local community. We recommend choosing empirically supported treatments that can then be adapted based on patient preferences, a reflection of program values; utilization, in consideration of economic resources; and outcomes. This approach provides a framework for training clinicians on structured interventions that they can then flexibly implement individually with patients and families.

A few examples from STEP of how we have changed inclusion criteria, interventions, and service delivery structure may illustrate. When we begin recruiting, our criteria included 'early in treatment' as defined by less than 12 weeks lifetime antipsychotic use. As this excluded many individuals who were recent onset, we later removed the weeks of antipsychotic use limit. Our initial set of interventions included Multifamily Group Psychoeducation and Support (MFG) [19] and provided an opportunity for clinicians to learn about the impact of expressed emotion and delivery of psychoeducation and problem solving techniques; however, participation rates were low and family members were more likely to attend single family sessions. Thus, we later implemented Family Focused Therapy (FFT) [20] which accommodated this apparent preference, reduced delays in offering the intervention as waiting for a group cohort to accumulate was no longer necessary, and added explicit teaching of communication and problem solving skills to the clinicians' skill set. Similarly, a Cognitive Behavioral Group (CBT) offered early on in STEP's development [21] provided an excellent opportunity for public mental health clinicians to hone their CBT skills to this population but was poorly attended. We later adopted the Social Cognition and Interaction Training (SCIT) group, which is engaging and interactive and with an explicit emphasis on socialization that appeals to our age group. Now that STEP clinicians have been trained and supervised on this model, they are able to incorporate SCIT techniques into the individual sessions of patients who are not willing or able to attend group. Due to resource limitations, in our first clinical trial, primary clinicians assisted patients in obtaining work or returning to school. We learned through patient feedback that emphasis on work and school were key to engagement. Increased resources from the State of Connecticut included dedicated Supported Employment and Supported Education staff. We suspect having designated staff who focus on vocational outcomes improves our appeal to our young adult clients and these roles allow for strengthening ties with potential employers, colleges and universities as well as provide valuable observations on how the patient is functioning in the community. Regarding service structure, we have changed from a combined clinician/outreach staffing to separate personnel dedicated to outreach and engagement. We have found that these tasks require extensive time in the community not typically practical for a clinician schedule in order to develop our referral network and strengthen ties with stakeholders who can facilitate hastening young people into care.

2.7. Justifying Services

Early adopters and more established programs may have concerns about funding and stakeholder commitment to CSC. Whatever processes and service delivery structures they chose, we encourage programs to orient their processes toward population health and invest in outcomes monitoring in support of demonstrating value to their funders [22]. For example, reducing hospitalizations and improving vocational engagement in STEP has helped justify committing financial resources.

3. CONCLUSION

Managers of resources in U.S. healthcare agencies are wise to consider implementing early intervention services for psychotic illnesses. Empirical evidence supports a clear benefit for comprehensive models of care in reducing distress, disability, and cost. This is reflected in ongoing national funding initiatives to support service implementation and pending legislation in the U.S. congress recognizing the importance of early intervention for psychotic illnesses. While there is much to celebrate in these developments, there is also much work to do. While CSCs have demonstrated unambiguous impact, they are insufficient to transform the trajectories of illnesses that have often begun long before and will persist long after the relatively brief period within a CSC. In many cases, disability has accrued well before the onset of reliably recognizable symptoms. The goal of early recognition at a prodromal or even premorbid phase remains an active aspiration for research that deserves vigorous support. Also, the impact of CSCs may not be sustained in the years after transition to usual care services [23] and new approaches are needed to sustain the positive effects of these services. Finally, while CSCs do include elements of community outreach, their focus is on the care of those who are able to respond to minimal efforts at early detection of incident cases. Focused efforts are required and underway to learn how to reduce the duration of untreated psychosis (DUP) [24]. The landmark Scandinavian TIPS study [25] was the first to demonstrate successful reduction of DUP, and notably this appeared to have a durable impact on outcome [26]. The development and testing of approaches to reduce DUP in the U.S. context, is the focus of several ongoing NIMH funded research efforts [24]. The ability to advance knowledge and practice in all these areas will be accelerated by the implementation of CSCs across the U.S. that can provide best practice care while also serving as necessary platforms for research that can our knowledge of the causes and physiology of psychotic illnesses and inform the next generation of interventions.

CONFLICT OF INTEREST

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SUPPLEMENTARY WORK S1

Results: Controls showed a lesser fronto-central pre-stimulus theta power (−2.512, $p=0.012$), which was negatively correlated with parietal beta ITC following target response (−0.679, $p=0.001$). This relationship was absent in patients (−0.165, $p=0.462$) and correlation difference ($p<0.05$). There was, however, no group difference in beta ITC (−0.439, $p=0.639$).
Conclusions: We present this relationship as a correlate of sensory–motor transformation, disrupted in schizophrenia without a manifest effect on beta ITC. Excess task-irrelevant activity (perhaps secondary to dopaminergic neuron-modulation of GABA and NMDA networks) could be causative.

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62 – IMPAIRED SYNCHRONIZATION OF NEURAL OSCILLATIONS IMMEDIATELY FOLLOWING AUDITORY STIMULI REPRESENTS A PERVASIVE DEFICIT IN BRAIN RECRUITMENT IN SCHIZOPHRENIA

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Background: Abnormal coordination of EEG oscillations has been associated with a range of psychopathology in schizophrenia. This could stem from a fundamental neuronal impairment, manifesting at a basic level of stimulus-assimilation. Post stimulus responses can be characterized by their phase relationship to stimulus onset; either generated from ongoing pre-stimulus activity or de novo. Winterer implicates an excess 'broadband noise' in behavioral impairments in patients. We propose that schizophrenia involves a deficit in neural recruitment, associated with increased pre-stimulus activity.
Methods: One hundred and twenty-eight channel EEG was recorded from 22 patients with DSM-IV criteria adolescent-onset schizophrenia and 22 age- and sex-matched controls undertaking a frequency deviant auditory oddball task. Data were segmented into 3-s epochs surrounding the non-target stimulus. Artefact was corrected using ICA before special-decomposition into the 5 bands (delta to gamma) using discrete windowed Fourier transforms. Inter-trial phase coherence and event-related spectral power (both stimulus-locked and non-locked) were derived. Fronto-central signal was examined in 3 windows: pre-stimulus (−525 to −275 ms), post-stimulus 0–250 ms and 250–500 ms.
Results: Patients showed a pan-spectral impairment in post-stimulus recruitment: a lesser percentage power increase, greatest in theta (−3.873, $p=0.000$); a significantly reduced consistency of phase organization across trials (−3.450, $p=0.001$); plus increased theta/delta pre-stimulus activity (−2.512, $p=0.012$/−2.30, $p=0.026$). The extent of stimulus-locked theta activity showed a strong positive correlation with pre-stimulus power in controls (0.589, $p=0.004$), which is disrupted in patients (0.200, $p=0.371$).
Conclusions: This study represents the first, such comprehensive demonstration of the impaired recruitment of oscillations in schizophrenia; an impairment, perhaps related to maladaptive pre-stimulus (structural or neuromodulatory via prefrontal dopamine) compensation.

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63 – INFLUENCE OF METAGLOSSOTHERAPY ON THE COGNITIVE EVENT-RELATED POTENTIALS OF SCHIZOPHRENIC PATIENTS

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Background: Metaglossotherapy (MGT) is a method of treating schizophrenic patients based on teaching them a new foreign language. The method was proposed by Dr. A. Matulis (1977, USA). During MGT the patient would once again initiate an activity of labeling, adopting to a "new" reality only with different foreign names. Besides the communicative amelioration, the new foreign language can contribute notably to the stabilization and clarification of the schizophrenic patient's self-concept and have an overall positive influence on schizophrenic patient's cognitive functions. Our goal was to evaluate the influence of MGT on the cognitive event-related potentials of treated schizophrenic patients.
Methods: A sample size of 11 long-stay male chronic schizophrenic patients took part in the program. The selected patients were assigned into two groups. One group was learning English, another group – Esperanto. The program lasted 3 months, 3 lessons a week. Auditory event-related potential (ERPs) were recorded at baseline and after 3 months of MGT. The ERPs were recorded with the digital EEG device from Fz, Cz and Pz sites. ERPs were acquired during active auditory oddball paradigm. Comparisons of peak latencies and amplitudes of ERPs N200, P300 components before MGT and after 3 months of therapy were performed.
Results: The amplitudes of both components slightly increased after 3 months of MGT. However, the differences were statistically not significant. The latencies of P300 component have significantly ($p=0.02$) shortened (for Cz electrode from 379.5 ms to 347.6 ms after MGT).
Conclusions: The tendency of shortening of P300 latency can be indicator of improvement in cognitive function, but it is necessary to measure ERPs for larger number of patients.

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64 – NEUROPSYCHOLOGICAL CORRELATES OF N400 ANOMALIES IN PATIENTS WITH SCHIZOPHRENIA

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Impaired Synchronisation of Neural Oscillations Immediately following Auditory Stimuli Represents a Pervasive Deficit in Brain Recruitment in Schizophrenia.

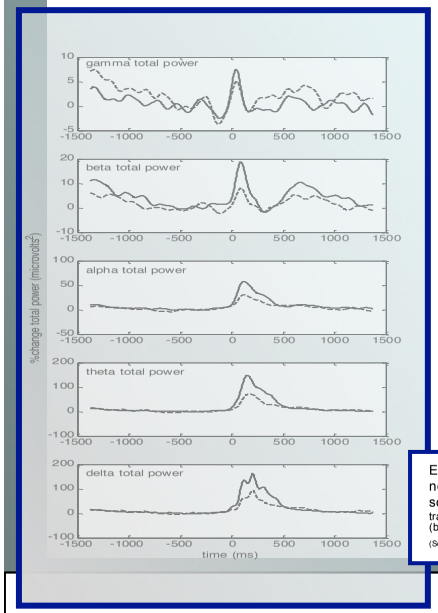
Cahill, J.D., Groom, M.J., Bates, A.T., Hollis, C., & Liddle, P.F.

Background

Abnormal coordination of EEG oscillations has been associated with a range of psychopathology in schizophrenia. This could stem from a fundamental impairment in the coordination and recruitment of neural networks.

An incoming stimulus may 'recruit' the brain via the generation (or enhancement) of oscillations either phase-locked to stimulus onset of endogenously generated phase. Both these processes seem to occur to produce the initial transient post-stimulus pan-spectral burst of power. The magnitude of the stimulus phase-locked activity (calculated across trials) may be affected by both the consistency of the phase-relationship to stimulus onset across trials and the amplitude of the phase locked signal at each trial.

Work by Winterer implicates an excess EEG 'broadband noise' related to behavioural impairments in patients. We hypothesis that schizophrenia involves a pan-spectral deficit in the degree of the initial neural recruiting response to simple attended stimuli, manifest in the following stimulus phase- and non phase-locked measures: *Evoked power* quantifies the activity which has a constant phase relationship to stimulus-onset across trials (dependant on amplitude and phase). *Inter-trial Coherence (ITC)* quantifies the degree of consistency of the phase relationship across trials, but is independent of amplitude and hence solely reflects phase-resetting. *Total power* quantifies all oscillatory activity irrespective of phase. *Induced power* is derived from the subtraction of the evoked activity from the total activity and is designed to quantify the oscillations without consistent stimulus phase-locking across trials. The ratio of evoked to induced is loosely referred to here as signal/noise ratio under the conventional premise that stimulus-locked activity task-related and non stimulus-locked is not.



Event-related synchronisation of neural activity is impaired in schizophrenia: Group spectral power traces showing post-stimulus ERS (baseline corrected)

(Solid lines = Controls, Dashed lines = Patients)

Methods

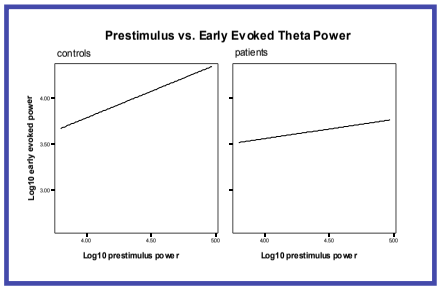
128 channel EEG was recorded from 22 patients with DSM-IV criteria adolescent-onset schizophrenia and 22 age and sex-matched controls undertaking a frequency deviant auditory oddball task. Data were segmented into 3 second epochs surrounding the non-target stimulus. Artefact was corrected using ICA before decomposition into the 5 bands (delta to gamma) using discrete windowed Fourier transforms. Inter-trial Phase Coherence and event-related spectral power (both stimulus-locked and non-locked) were derived. Fronto-central signal was examined in 3 windows: pre-stimulus (-525 to -275ms), post-stimulus 0-250ms and 250-500ms.

Results

All subjects show a transient pan-spectral burst of activity consisting of both stimulus phase-locked and non phase-locked activity. The initial increase in ITC as well as induced power lends support to (though does not confirm) the occurrence of both amplitude perturbation and phase-resetting in recruiting the brain.

Table of t values, controls vs. patients (p=<0.01**,p=<0.05*,p=<0.1#)

	Delta	Theta	Alpha	Beta	Gamma
%Change Total Power *0-250ms*	4.052**	4.627**	2.822**	2.297*	0.207
250-500ms	3.204**	3.092**	1.287	0.094	-1.454
Log Evoked Power *0-250ms*	2.330*	2.681*	2.752**	3.536**	0.859
250-500ms	2.141*	2.039*	1.300	-0.221	-0.290
ITC *0-250ms*	3.569**	3.933**	3.534**	2.995**	1.914#
250-500ms	5.029**	4.410**	2.227*	1.147	0.057
Signal to Noise Ratio *0-250ms*	3.445**	3.982**	3.662**	3.854**	0.902
250-500ms	3.927**	3.746**	2.043*	-0.017	-0.321
%Change Induced Power *0-250ms*	2.132*	2.346*	1.440	1.114	-0.437
250-500ms	2.591*	2.535*	0.699	-0.023	-1.500
Log Pre-stimulus Power *-525 to -275ms*	-2.732**	-2.904**	-1.007#	-0.854	-0.150



Pearson's Correlations

Controls: 0.582 (p=0.004)

Patients: 0.169 (p=0.452)

Group difference: p=0.126

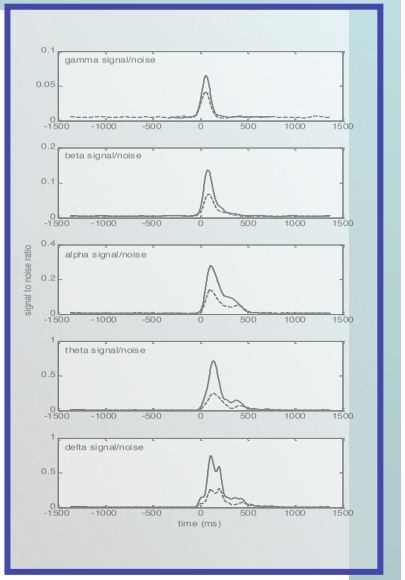
(when controlled for pre vs. ITC correlation, group difference: p=0.012)

Main Findings

- Patients show a relative impairment in all post-stimulus spectral measures:
  - A lesser percentage power increase, greatest in theta, continuing into beta (as a trend);
  - A reduced consistency of phase organization across trials in all bands to at trend significance;
  - Reduced evoked power and signal to noise ratio from delta up to beta bands;
  - Reduced induced power in the delta and theta bands.
- Patients also show increased theta/delta pre-stimulus power which does not significantly confound the above effects.
- This pre-stimulus activity shows differential relationships with stimulus-locked responses between groups – to be elaborated elsewhere.

The ratio of evoked to induced power is decreased in schizophrenia: post-stimulus signal/ noise ratio across the spectrum

(Solid lines = Controls, Dashed lines = Patients)



Discussion

This study considers whether a basic deficit in neural recruitment underlies the growing literature showing decreased event-related and increased resting oscillations in schizophrenia. Perhaps the primary deficit lies in the ability of neural oscillators to entrain other functionally relevant assemblies in response to external stimuli.

Explanations for the increased baseline low frequency activity observed in patients already exist. Although, the analysis of pre-stimulus power and its post-stimulus correlates across subjects poses methodological and conceptual challenges.

Llinas' proposes pathological cyclic hyper-polarization of relay neurons (as seen in sleep) leads to periodic bursts in the theta band through deactivation of T-type calcium channels and feedback inhibition by thalamic reticular nucleus neurons in schizophrenia. It remains to be proved whether the abnormal background activity in schizophrenia is a cause or attempted compensation for a deficit in recruitment. The compensation theory is conceptually supported by work by Grace et al.; suggesting an increased prefrontal *tonic* dopamine release compensating for impaired *phasic* release. Cho also suggests that theta and alpha activity compensate for a lack of gamma modulation with cognition.

Conclusion

Oscillatory analysis of the EEG has opened a new dimension in schizophrenia research, which lends itself well to the conception of schizophrenia as a disorder with a fundamental deficit in brain recruitment at its core. Although EEG findings may be linked with biological findings in schizophrenia, the origins and functional significance of EEG measures remain theoretical.

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SUPPLEMENTARY WORK S2

well. Progress in social cognitive measures, in particular emotional face recognition, is supported by evoked potential response that shows an activation of medio-frontal areas (typically involved in emotional stimuli processing) and this suggests that the core circuitry for imitation might interact with the limbic system during social mirroring.
Conclusions: These preliminary results need confirmation from the larger ongoing study rehabilitation treatment for schizophrenics based on imitation of social cognition skills. However, if the preliminary results are confirmed, action observation and imitation could be regarded as a new frontier in rehabilitation, easy to implement and with a well-founded neurophysiologic basis.
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EEG Studies

60 – CORRELATION BETWEEN THE EFFECTS OF SECOND GENERATION ANTIPSYCHOTIC DRUGS AN THE EVENT-RELATED POTENTIALS (ERPS) P300, P50 AND PANSS NEGATIVE SCORE: A PRELIMINARY STUDY

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Background: The P300 component of the ERP reflects the capacity of self-organisation and self-regulation of the central nervous system. The P50 suppression reflects the capacity to interpret a stimulus as negligible.
Methods: Fifty-five individuals (32 males and 23 females; mean age=35.9 years [SD=13.8]) meeting DSM-IV criteria for schizophrenia, admitted for an acute relapse, were included in the study and observed within the 8-month period from 2005/10 to 2006/07. They were treated with the following antipsychotics (mean daily dosage): aripiprazole (13.75 mg), risperidone (5.06 mg), olanzapine (14.12 mg), amisulpride (1000 mg) and clozapine (150 mg). The other psychotropic drugs were prohibited except for cyamemazine (100 mg/day during the first week), benzodiazepines, zolpidem and anticholinergic medications. Clinical and electrophysiological evaluations were performed before the start of treatment (T_1) and after remission (T_2). Psychopathology was measured by the Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS).
Results: After treatment, P300 latency was not significantly improved but we observed a significant increase in P300 amplitude ($p<0.02$). P50 suppression deficit, which was present in 49 subjects at T_1, was observed in only 44 patients at T_2 ($p<0.003$). This improvement occurred particularly in patients receiving aripiprazole or risperidone. PANSS and BPRS decreased respectively from 100±12 and 85±8 at T_1 to 53±11 and 38±6 at T_2 ($p<0.01$) .This study will analyze these results with the items of the negative scale of the PANSS and try to show the difference between each treatment for positives effects on specific cognitive functions.
Conclusions: Correlation between PANSS and ERP evaluation may suggest that clinical cognitive symptomatology relies to electrophysiological measurement. The negative scale of the PANSS decreased with the treatment but is not able to value differences for each treatment and for specific cognitive functions. ERP evaluation may help psychiatrists in the choice of the optimal drug to treat schizophrenic patients. We need another evaluation than the negative scale of the PANSS to measure the improvement on specific cognitive functions.
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61 – PRE-STIMULUS THETA POWER PREDICTS THE SUPPRESSION OF BETA SYNCHRONIZATION DURING MOTOR RESPONSE: DOES A DISRUPTED EFFECT IN SCHIZOPHRENIA REFLECT PATHOLOGICAL BASELINE THETA ACTIVITY?

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Background: Although aberrant non-stimulus locked background activity has been demonstrated in schizophrenia, the significance of pre-stimulus EEG remains unknown. A disrupted relationship between pre- and post-stimulus oscillations might reflect poor cerebral recruitment in schizophrenia. Excess low frequency activity has already been demonstrated at rest and preceding stimulus processing. Beta power is negatively related to motor events. Imperative stimuli may suppress the initial, indiscriminate, post-stimulus beta phase synchronization via parieto-dependant motor networks. Theta activity associated with attention and working memory tasks may facilitate stimulus-assimilation. It is hypothesized that the extent of pre-stimulus theta will negatively predict the extent of parietal beta inter-trial phase coherence (ITC) around response. This relationship will be disrupted in schizophrenia.
Methods: One hundred and twenty-eight channel EEG was recorded in 22 patients with DSM-IV criteria adolescent-onset schizophrenia and 22 age/sex-matched controls whilst undertaking a frequency deviant auditory oddball task necessitating a button press. Data were segmented into 3-s epochs around the stimuli. Artefact was corrected using ICA before decomposition into theta (4–8 Hz) and beta (13–30 Hz) bands using discrete Fourier transforms. ITC and total power were calculated for fronto-central and midline-parietal regions: pre-stimulus window (−525 to −275 ms) and response window (250–500 ms).

Results: Controls showed a lesser fronto-central pre-stimulus theta power (−2.512, $p=0.012$), which was negatively correlated with parietal beta ITC following target response (−0.679, $p=0.001$). This relationship was absent in patients (−0.165, $p=0.462$) and correlation difference ($p<0.05$). There was, however, no group difference in beta ITC (−0.439, $p=0.639$).
Conclusions: We present this relationship as a correlate of sensory–motor transformation, disrupted in schizophrenia without a manifest effect on beta ITC. Excess task-irrelevant activity (perhaps secondary to dopaminergic neuron-modulation of GABA and NMDA networks) could be causative.

doi:10.1016/j.schres.2007.12.128

62 – IMPAIRED SYNCHRONIZATION OF NEURAL OSCILLATIONS IMMEDIATELY FOLLOWING AUDITORY STIMULI REPRESENTS A PERVASIVE DEFICIT IN BRAIN RECRUITMENT IN SCHIZOPHRENIA

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Background: Abnormal coordination of EEG oscillations has been associated with a range of psychopathology in schizophrenia. This could stem from a fundamental neuronal impairment, manifesting at a basic level of stimulus-assimilation. Post stimulus responses can be characterized by their phase relationship to stimulus onset; either generated from ongoing pre-stimulus activity or de novo. Winterer implicates an excess 'broadband noise' in behavioral impairments in patients. We propose that schizophrenia involves a deficit in neural recruitment, associated with increased pre-stimulus activity.
Methods: One hundred and twenty-eight channel EEG was recorded from 22 patients with DSM-IV criteria adolescent-onset schizophrenia and 22 age- and sex-matched controls undertaking a frequency deviant auditory oddball task. Data were segmented into 3-s epochs surrounding the non-target stimulus. Artefact was corrected using ICA before special-decomposition into the 5 bands (delta to gamma) using discrete windowed Fourier transforms. Inter-trial phase coherence and event-related spectral power (both stimulus-locked and non-locked) were derived. Fronto-central signal was examined in 3 windows: pre-stimulus (−525 to −275 ms), post-stimulus 0–250 ms and 250–500 ms.
Results: Patients showed a pan-spectral impairment in post-stimulus recruitment: a lesser percentage power increase, greatest in theta (−3.873, $p=0.000$); a significantly reduced consistency of phase organization across trials (−3.450, $p=0.001$); plus increased theta/delta pre-stimulus activity (−2.512, $p=0.012$/−2.30, $p=0.026$). The extent of stimulus-locked theta activity showed a strong positive correlation with pre-stimulus power in controls (0.589, $p=0.004$), which is disrupted in patients (0.200, $p=0.371$).
Conclusions: This study represents the first, such comprehensive demonstration of the impaired recruitment of oscillations in schizophrenia; an impairment, perhaps related to maladaptive pre-stimulus (structural or neuromodulatory via prefrontal dopamine) compensation.

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63 – INFLUENCE OF METAGLOSSOTHERAPY ON THE COGNITIVE EVENT-RELATED POTENTIALS OF SCHIZOPHRENIC PATIENTS

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Background: Metaglossotherapy (MGT) is a method of treating schizophrenic patients based on teaching them a new foreign language. The method was proposed by Dr. A. Matulis (1977, USA). During MGT the patient would once again initiate an activity of labeling, adopting to a "new" reality only with different foreign names. Besides the communicative amelioration, the new foreign language can contribute notably to the stabilization and clarification of the schizophrenic patient's self-concept and have an overall positive influence on schizophrenic patient's cognitive functions. Our goal was to evaluate the influence of MGT on the cognitive event-related potentials of treated schizophrenic patients.
Methods: A sample size of 11 long-stay male chronic schizophrenic patients took part in the program. The selected patients were assigned into two groups. One group was learning English, another group – Esperanto. The program lasted 3 months, 3 lessons a week. Auditory event-related potential (ERPs) were recorded at baseline and after 3 months of MGT. The ERPs were recorded with the digital EEG device from Fz, Cz and Pz sites. ERPs were acquired during active auditory oddball paradigm. Comparisons of peak latencies and amplitudes of ERPs N200, P300 components before MGT and after 3 months of therapy were performed.
Results: The amplitudes of both components slightly increased after 3 months of MGT. However, the differences were statistically not significant. The latencies of P300 component have significantly ($p=0.02$) shortened (for Cz electrode from 379.5 ms to 347.6 ms after MGT).
Conclusions: The tendency of shortening of P300 latency can be indicator of improvement in cognitive function, but it is necessary to measure ERPs for larger number of patients.

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64 – NEUROPSYCHOLOGICAL CORRELATES OF N400 ANOMALIES IN PATIENTS WITH SCHIZOPHRENIA

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Pre-stimulus Theta Power predicts the Suppression of Beta Synchronization during Motor Response: Does a disrupted Effect in Schizophrenia reflect Pathological baseline Theta Activity?

Cahill, J.D., Groom, M.J., Hollis, C., & Liddle, P.F.

Background

Building on the oscillatory analysis of the resting state in schizophrenia, recent findings from our lab have prompted an exploration of relationships between fronto-central pre-stimulus low frequency power (perhaps reflecting attentive preparation in thalamo-cortical loops) and post-stimulus spectral perturbations (hypothesised as disrupted in schizophrenia). The beta band effects surrounding the motor response is one candidate phenomenon.

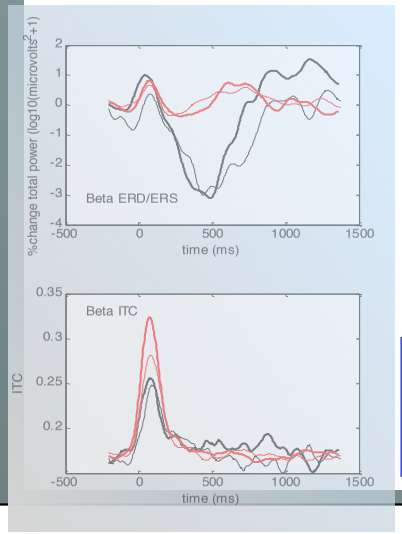
Event-related Desynchronisation (ERD) in the beta band (13-30Hz) has been demonstrated in cortical and sub-cortical sources, peaking at average response time (1). It is likely to reflect a release of motor networks from tonic inhibition into action, and is followed by a rebound Event-related Synchronisation (ERS). A useful and comprehensive way of describing event-related spectral effects is through both change in total power, irrespective of stimulus-phase relationships (ERD/ERS) and the Inter-trial Phase Coherence (ITC, a measure of the consistency of phase relative to stimulus-onset across trials - independent of amplitude). The Beta ITC coincident with the beta ERD has not been well characterised and may be a better indicator of the process of 'sensory-motor transformation' (the triggering of a learnt motor response via parieto-dependant motor networks by an appropriate stimulus (2)).

This study aims to explore the relationship between pre-stimulus fronto-central theta power and parietal beta activity around the time of motor response to an oddball target stimulus.

Controls with a higher degree of endogenous baseline phase synchrony tend to show less consistent phase-synchrony across trials. Does this relationship manifest during motor response in beta and is it weakened in schizophrenia?

Methods

128 channel EEG was recorded in 22 patients with DSM-IV criteria adolescent-onset schizophrenia and 22 age/sex-matched controls whilst undertaking a frequency deviant auditory oddball task necessitating a button press.



Data were segmented around the stimuli. Artefact was corrected using ICA before decomposition into theta (4-8Hz) and beta (13-30Hz) bands using discrete Fourier transforms. ITC and total power were calculated for fronto-central and midline-parietal regions. The pre-stimulus window was defined as -525 to -275ms. The peri-response period was divided into 4 windows guided by 2 s.d. around mean response time.

Plots of Beta event related power changes and Inter-trial Coherence over time, group and condition.

Thick = Controls

Thin = Patients

Black = Targets (response)

Red = Non-targets

Results

Power values were log10 transformed for normality, ERD/ERS was expressed as a percent change from baseline. Repeated measures ANOVAS were used to compare means and Pearson's coefficients for correlations. The significance of correlation differences were estimated via a Fisher Z transform.

		Pre Response (80 to 280 ms)		Early Response (280 to 480 ms)		Late Response (480 to 680 ms)		Post Response (680 to 880 ms)	
		ITC	ERD	ITC	ERD	ITC	ERD	ITC	ERD
Beta ITC /ERD Magnitude (F with p values bracketed)	*Condition Effect*	6.340 (0.016)	3.349 (0.074)	1.917 (0.174)	28.53 (0.000)	0.306 (0.583)	32.79 (0.000)	0.191 (0.665)	4.145 (0.048)
	Group Effect	0.063 (0.803)	0.114 (.737)	0.000 (0.994)	0.461 (.501)	3.330 (0.075)	0.286 (0.596)	2.143 (0.151)	2.162 (0.149)
	Group Condition Interaction	1.803 (0.187)	0.003 (0.954)	0.361 (0.551)	0.018 (.893)	1.875 (0.178)	0.160 (0.691)	9.272 (0.004)	2.415 (0.128)
Theta/Beta Correlation Targets (Pearson's Coeff., P values bracketed)	*Controls*	-0.244 (0.273)	-0.030 (0.893)	-0.628 (0.002)	-0.111 (0.623)	-0.368 (0.092)	-0.433 (0.044)	-0.319 (0.148)	-0.285 (0.198)
	Patients	-0.134 (0.551)	0.194 (0.386)	0.045 (0.844)	-0.050 (0.825)	-0.590 (0.004)	-0.016 (0.944)	0.038 (0.866)	-0.016 (0.944)
	Group Difference	0.726	0.484	0.032	0.849	0.368	0.168	0.254	0.3953
Theta/Beta Correlation Non-targets (Pearson's Coeff., p values bracketed)	*Controls*	-0.503 (0.017)	-0.208 (0.353)	0.138 (0.540)	-0.223 (0.319)	-0.218 (0.329)	-0.272 (0.221)	-0.037 (0.871)	-0.194 (0.386)
	Patients	-0.283 (0.202)	0.055 (0.808)	-0.161 (0.474)	0.315 (0.154)	-0.352 (0.108)	0.139 (0.536)	-0.309 (0.162)	0.095 (0.673)
	Group Difference	0.418	0.412	0.352	0.089	0.652	0.197	0.384	0.368

Main Findings

•There was no significant group difference in reaction time or performance.

•Both groups show a suppression of parietal beta power throughout the peri-response period.

•Beta ITC shows an immediate burst which is suppressed coincidentally with total power. This burst is smaller to the target tone (perhaps reflecting a less well established response to the rarer tone resulting in increased jitter).

•A low level of ITC appears to remain which shows no difference between conditions, implying (though not confirming) that the magnitude of beta ITC is not indicative of the motor response.

•There is, however, a divergence in ITC between groups culminating in a group/ condition interaction in the post response period (controls retaining and patients lowering ITC).

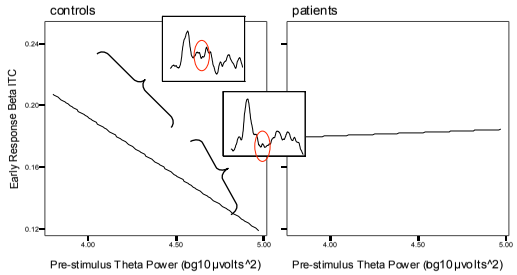
•The relationship of interest (pre-stimulus theta vs. beta ITC) manifests in controls' immediate ITC burst following non-target tones. This correlation is weakened to non-significance in the target condition – perhaps reflecting additional processes contributing to the magnitude of this burst (e.g. recognition of rarer target tone).

•The relationship of interest, however, manifests during the motor response to the target and is significantly different between the groups in the early response window.

•The relationship manifests later and less consistently in the patients than controls, however there is no significant delay in reaction times.

•Controls with greater pre-stimulus theta show greater beta power (lesser ERD) in the ascending part of the motor response suppression

Pre-stimulus Theta Power vs. Early Response Beta ITC



There is a negative relationship between baseline theta and early response beta ITC between controls. Could this a spectrum of preferential use of phase-resetting for brain recruitment? The beta ITC 'high responders' show a shouldering following the initial ITC burst, whereas 'low responders' do not.

Discussion

Limitations of this study include the differing trial numbers between condition (15% target trials) and the reduced signal to noise ratio associated with the higher frequencies of the EEG.

Increased variability in the patient data must be considered in interpreting the lack of significant correlations, however, this does not explain the apparently delayed appearance of the theta/beta relationship until 480 to 680ms. Could aberrant baseline theta circuit activity (perhaps modulated by dopamine) be disrupting these relationships?

Pre-stimulus fronto-central theta power may reflect a state of attentive preparation, which, through facilitating neural recruitment, shows a spectrum of post-stimulus correlates in health. Beta ITC could be one such correlate perhaps reflecting the process of sensory-motor transformation in parieto-motor networks.

A range of effects are described here and it is a challenge to estimate their biological basis. Further work is indicated to develop this type of analysis.

Conclusion

It can be broadly concluded that controls seem to show with modest consistency certain relationships between pre-stimulus theta power and beta ITC, which becomes masked at certain points. Patients with schizophrenia show weakened or more unpredictable relationships.

The investigation of the relationship between pre and post stimulus activity is fraught with challenges, however, may prove illuminating in schizophrenia especially in high functioning patient groups such as this where less sensitive EEG measures may be normal.

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SUPPLEMENTARY WORK S3

Cannabinoids increase neural noise in humans: a nonlinear analysis of EEG signals

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Introduction

Cannabinoids and neural noise

- Legalization of medical and recreational cannabis, increasing potency of cannabis, and recreational use of highly potent cannabinoids (e.g. K-2), warrant study of how cannabinoid receptor type 1 (CB1R) activation affects information processing.
- Endocannabinoids (eCBs) released by postsynaptic neurons act as retrograde messengers and reduce the release of neurotransmitters (glutamate or GABA) by presynaptic neurons by activating CB1Rs localized on their terminals (Kano et al., 2009).
- During task performance, pyramidal cells strongly recruited (activated) by the task release eCBs which inhibits GABA inhibition from interneurons, thereby, further increasing the activation of these pyramidal cells (Bartos & Elgueta, 2012).
- In contrast, weakly recruited (activated) pyramidal cells do not release eCBs thus maintaining the GABA-mediated inhibition from interneurons (Bartos & Elgueta, 2012).
- It has been argued that this CB1R-mediated mechanism increases the signal-to-noise ratio of neural circuits by removing inhibition from task-relevant neurons (signal carriers) while keeping the activity of task-irrelevant neurons (random noise) suppressed.
- Exogenous cannabinoids disrupt this mechanism by equally disinhibiting both signal-carrying and noise-generating neurons, increasing the noise level of the network's transmission of information.

Measuring neural noise:

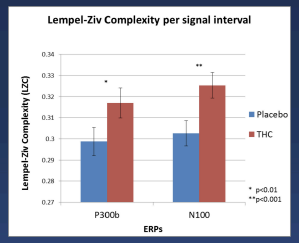
- Lempel-Ziv Complexity (LZC) is a nonlinear information theory measure developed to characterize the randomness or level of *noise* of finite length sequences (Lempel & Ziv, 1976). For random sequences (e.g. white noise) it approaches 1, while for regular (periodic) sequences it approaches 0 (Aboy et al, 2006; Hu et al., 2006).
- LZC has been used for characterizing brain dynamics in altered levels of consciousness and several neuropsychiatric disorders including psychotic disorders (Casali et al., 2013; Fernandez et al., 2010). However, it has never been used to study cannabinoid-induced alterations in information processing
- LZC was chosen as a biomarker of neural noise over SNR because it is not derived from trial averaging but directly from the EEG data, ruling out the possibility that observed noise resulted from increased intertrial peak latency jitter (random latency) and not from random activity (random content) per se.

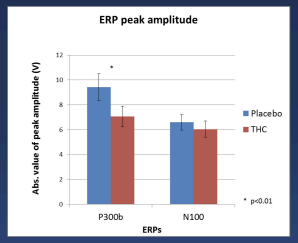
Hypothesis

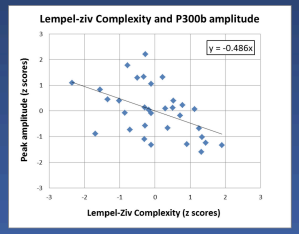
- The CB1R agonist delta-9-tetrahydrocannabinol (THC) will increase neural noise (LZC) in the EEG signals of healthy humans during task performance (P300).
- THC-induced increased LZC (noise) will correlate with the THC-induced reductions in target P300 (P300b) amplitude.

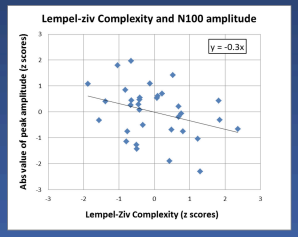
Methods

- Healthy volunteers (n=21) received a low dose of intravenous THC (0.015mg/kg) or placebo over 10 minutes in a double-blind, randomized, crossover design over 2 test days as part of a larger study.
- EEG data were registered during peak drug effects while subjects performed an auditory oddball task reported in D'Souza et al. (2012).
- EEG data were analyzed using standard procedures plus muscle artifacts removal with a canonical correlation blind source separation technique (De Clercq et al, 2006).
- Generalized estimating equations (GEE) were used to account for data correlations due to repeated measures.









Results

- The THC condition showed significantly higher LZC values compared to placebo during the P300b time interval (250-500ms) at electrode Pz (Wald X2=7.574, p=0.006) and during the N100 interval (1-250ms) at electrode FCz (Wald X2=16.004, p<0.001).
- Consistent with a previous study from our group (D'Souza et al., 2012) , P300b peak amplitude was significantly smaller during the THC condition compared to placebo (Wald X2=4.490, p=0.034) and no significant differences were found for the N100 (Wald X2=0.565, p=0.452).
- Significant inverse correlations (standardized regression coefficients) were found between LZC and the amplitude of both P300b (β=-0.486, Wald X2=13.156, p<0.001) and N100 (β=-0.300, Wald X2=4.443, p=0.035).

Conclusions

- This is the first study to show in humans that THC at doses that produce psychotomimetic effects, acutely increases neural noise and that this measure is inversely correlated with the amplitude of P300b, which is known to be disrupted by THC (D'Souza et al., 2012), and N100.
- Characterizing the acute effects of exogenous cannabinoids on neural noise in humans, might further our understanding of the neural correlates underlying the information processing abnormalities induced by these compounds and the neural mechanism of states associated with abnormal levels of neural noise such as psychosis (Winterer & Weinberger, 2000).
- The high rates of cannabis use and the legalization of medical and recreational cannabis, warrant further study of the long term effects of increased noise on the architecture and functionality of neural networks, and if these effects contribute to the development of neuropsychiatric disorders.

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John D. Cahill, September 2017

Session: 150-**Poster Session 3 - Saturday**

Saturday, May 10, 2014, 5:00 PM - 6:30 PM

Presentation: 1211 - **Cannabinoid Generate Neural Noise in Humans: A Nonlinear Analysis of EEG Signals**

Location: Americas Hall I - 3rd Floor

Pres. Time: Saturday, May 10, 2014, 5:00 PM - 6:30 PM

Category: Cognitive neuroscience

Keywords: cannabinoids; THC; CB1; psychosis; EEG

Author(s): **Jose A. Cortes-Briones**[1,2,3], John D. Cahill[1,3], Patrick D. Skosnik[1,3], Rajiv Radhakrishnan[1,2,3], Richard A. Sewell[1,2,3], Michelle Carbuto[1,2,3], Ashley Schnakenberg[1,3], Ashley Williams[1,3], Fred Bois[1,3], Mohini Ranganathan[1,2,3], Deepak C. D'Souza[1,2,3]

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Abstract: **Background**: Abnormally high levels of background brain activity -neural noise- is believed to play an important role in neuropsychiatric conditions, e.g., psychosis. The cannabinoid receptor 1 (CB1R) systems may contribute to the generation of aberrant noise. In this study we explored the effects of CB1R activation on neural noise in humans, and the relationship between neural noise and event related potentials known to be altered in neuropsychiatric conditions.
Methods: Healthy volunteers (n=21) received intravenous delta-9-tetrahydrocannabinol (THC) the CB1R partial agonist (0.015mg/kg) or placebo over 10min in a double-blind, randomized, crossover design. Electroencephalographic (EEG) data were registered while the subjects performed an oddball task. Neural noise was assessed with nonlinear measures of signal randomness.
Results: The THC condition significantly increased (p=0.018) noise relative to placebo. Furthermore, THC-induced noise was negatively correlated with the amplitudes of the N100 (r=-0.791, p=0.00004) and P3b (r=-0.461, p=0.027) ERPs.
Conclusions: In humans, CB1R activation by exogenous cannabinoids increases background neural noise. The latter is related to a number of ERPs known to be altered in neuropsychiatric disorders. The extent to which the noise generating effects of THC on information processing contributes to its behavioral and cognitive effects warrants further study.

SUPPLEMENTARY WORK S4

Topic one: Psychiatry (582000)

Topic two: Pharmacology/pharmacy/antibiotics (613000)

Ketamine and depression

The world of medicine has long known ketamine hydrochloride to be a dissociative anesthetic agent, typically used intravenously for pediatric surgical procedures. Ketamine's principal action in the brain is on *N*-methyl-D-aspartate (NMDA) receptors, where it blocks the action of the brain's principal excitatory neurotransmitter, glutamate.

As a derivative of phencyclidine (PCP), ketamine (**Fig. 1**) shares some notoriety as a commonly abused club drug, going under the street names K and Special K. It is a schedule III controlled substance in the United States. At lower, so-called subanesthetic doses (at which consciousness is largely preserved), ketamine produces dissociative (out-of-body) and hallucinogenic effects. These effects led to its early study in psychiatric research, as a pharmacological model of psychosis.

Depression, antidepressants, and treatment resistance.

Major depressive disorder is defined as a depressed mood or a loss of pleasure in daily activities consistently for at least a two-week period. There is a decline in social, occupational, or educational functioning. Depression remains one of the most significant causes of disability and lost productivity worldwide.

Medications, neuromodulatory treatments, psychotherapy, and social interventions potentially play an important role in the treatment of depression. Nevertheless, it is estimated that more than one-third of patients treated for depression will not adequately improve. Treatment resistant depression (TRD) is generally diagnosed when a patient has not derived significant clinical benefit from two or more adequate trials of conventional antidepressant medications.

When selecting any psychiatric medication, patients and their prescribers must weigh the potential benefits versus risks. The great suffering of people with TRD can justify the use of more efficacious treatments that carry greater risk. Lesser-used antidepressants and combinations of medications may be employed. Electroconvulsive therapy (ECT) is currently the most effective, validated treatment for TRD.

A paradigm shift.

Since the 1950s, when the serendipitous finding of the antidepressant effects of antituberculous drugs prompted a focus on the monoamine neurotransmitters, serotonin and norepinephrine, the formulary (list of prescribed drugs) for depression has steadily grown. However, until recently, novel antidepressant agents continued to focus on monoamine neurotransmitter systems without a significantly increased efficacy (albeit there was improved tolerability). Ketamine has now significantly broken that mold, leading to new frontiers in both the pathophysiology and treatment of depression.

At the end of the twentieth century, growing laboratory evidence for the role of NMDA receptor antagonists in depression began to coincide with serendipitous observations that

subanesthetic ketamine (given as an anesthetic or analgesic) reduced comorbid depressive symptoms in patients. The first systematic, placebo-controlled clinical trial of ketamine for major depression was conducted at Yale University School of Medicine (New Haven, CT) in 2000.

Ketamine has distinguished itself from conventional antidepressants through its rapid effect (4 hours versus 2 weeks), its efficacy (2 out of 3 patients respond versus 1 out of 2), and its hypothetical mechanism of action (glutamatergic systems versus monoaminergic systems). Unfortunately, the benefits are transient, tending to last less than a week. There is also the potential for its abuse and for a range of adverse effects. Therefore, clinical trials of ketamine have tended to study subjects with TRD; who have a favorable risk/benefit ratio.

Clinical trials.

Until recently, the evidence for ketamine's antidepressant effect in humans has primarily consisted of case reports or non-placebo-controlled (open-label) studies, which are potentially subject to bias. It is only in the past few years that research groups (including those from the National Institute of Mental Health and Mount Sinai School of Medicine) have added a handful of placebo-controlled trials, which more strongly support the clinical effects of ketamine.

There is a range of clinical evidence in humans to date; the majority of patients studied since 2011. A dozen case studies, totaling 16 patients, report a rapid antidepressant response with regimens ranging from one to six ketamine infusions. Durations of response range from a

day to several weeks. Open-label studies more systematically illustrate the effect of ketamine, but lack a placebo/control comparison. A dozen such studies, involving 120, mostly un-

medicated, treatment resistant depressed patients, most clearly support a rapid, transient response in approximately 40-60% of patients, at four hours after a single 0.5mg/kg intravenous infusion. Two further open-label studies have tested repeated dose regimens in a total of 34 subjects, showing a response rate of 50 to 71% and an extended median duration of effect of 18 days (after last infusion). Controlled-trials in this field have also been supportive of an effect, commonly comparing the response of ketamine and a non-psychoactive, saline placebo within each subject. There have been 6 such trials published, involving 81 depressed patients (including bipolar depression), showing a peak response rate ranging from 40 to 79% within 72 hours of a single IV administration. Finding a rigorous control condition is a challenge with ketamine - which has both an immediate intoxicating and downstream antidepressant effect. Results of ongoing trials using a psychoactive control, midazolam should be informative.

These trials have focused on a single, intravenous infusion (lasting 40 minutes) of racemic ketamine hydrochloride (at a dose of 0.5 mg per kg body weight). Clinical targets have mainly been subjects suffering from TRD (including those unresponsive to ECT), bipolar depression (major depression in the context of bipolar disorder), and suicidal ideation.

Attempts to extend the fleeting benefits of single-dose ketamine with an oral NMDA receptor antagonist, riluzole, proved ineffective. However, there is hope of sustaining ketamine's effect through repeated intravenous dosing regimens, which would be similar to the way that ECT is administered (three treatments per week with tapering frequency). Alternative routes of administration, particularly intramuscular, may also be of interest.

Another conceptually appealing application has been the use of ketamine as the anesthetic agent for ECT treatments. This, in fact, has been long practiced when struggling to induce therapeutic seizures in a patient. Ketamine will not increase the seizure threshold as much as conventional anesthetics. Sadly, the evidence for a cumulative benefit of ECT and ketamine is not compelling. The mechanism of interaction of these two treatments remains unclear, and it is likely that ketamine's antidepressant effect is particular to the lower, subanesthetic dose range.

Although a compelling novel mechanism for treating depression with ketamine is elucidated, practicality and safety may constrain the clinical utility of ketamine to a jump start for other biological, psychological, and social interventions.

Mechanism of action.

Recent investigations into the potential mechanism of action of ketamine have brought about a breakthrough, extending our understanding of the pathophysiology of depression as a whole. It has long been thought that chronic stress, associated with depression, may damage neurons (especially in the hippocampus and the rest of the limbic system), reducing the number of connections (synapses) between them. Laboratory studies in rodent models of depression show that a single ketamine dose induces a rapid behavioral response (equivalent to an antidepressant response), which is correlated with a rapid increase in the protein building blocks, number, and function of the synaptic connections in the prefrontal cortex (a brain region associated with mood and higher cognitive function) [**Fig. 2**].

By consolidating these various findings, investigators have proposed a model in which ketamine transiently reverses the synaptic deficits in the prefrontal cortex (**Fig. 3**). Brain-derived neurotrophic factor (BDNF) is a protein secreted to promote the normal growth of neurons and the formation of synapses (synaptogenesis). It is an important player for maintaining the balance of neurochemical factors necessary for synaptic function and regular mood (synaptic homeostasis). A component of this healthy equilibrium is the cycling of glutamate A1 (GluA1) receptors to and from the synapse, making the receptors functionally available. The depression state is characterized by a disruption of the equilibrium (synaptic destabilization), and GluA1 receptors are internalized and become unavailable at the synapse. Furthermore, BDNF levels were shown to be reduced in stress and depression, causing synapse loss and neuronal atrophy.

Ketamine's primary action is the blockade of NMDA receptors on inhibitory (GABAergic) interneurons, unleashing a burst of glutamate into the synapse. The glutamate acts on AMPA receptors (glutamate receptors that also bind the glutamate agonist AMPA) to signal a complex interplay of neurochemical factors (including BDNF, mTOR, TrKB, and Akt) [Fig. 3]. The end result is the restoration of GluA1 cycling and functional synaptic connections (synaptogenesis). Additionally, ketamine (through the inhibition of postsynaptic NMDA receptors) may deactivate an enzyme called eukaryotic elongation factor 2 kinase, disinhibiting the rapid production of synaptic proteins such as BDNF. BDNF levels are increased by a range of proven antidepressant treatments, including ketamine.

Vitally, this model accounts for the relative rapidity of ketamine's effects. Ketamine's eventual disinhibition of BDNF release (along with other essential components for functional

synapses) utilizes an ever-ready, efficient physiological mechanism for generating synaptic connections. This stands in contrast to conventional antidepressants, which are thought to rely on more extensive changes in the neuronal architecture.

A word of caution.

Reports of ketamine's potential clinical benefits must be interpreted with the utmost caution. Any therapeutic use of ketamine for depression is experimental, requires hospital monitoring, and has not received the general approval from the U.S. Food and Drug Administration. Furthermore, the unsupervised, nonprescription use of this drug is extremely dangerous and can be fatal. Acute adverse effects include increased heart rate and blood pressure, dangerous behavioral changes, and disturbing perceptual changes. Chronic side effects include ulcerative cystitis, cognitive and memory impairments, liver damage, structural brain damage, and drug abuse or dependence.

Future outlook.

The last few years have brought a wave of laboratory studies and clinical trials that augment our theoretical and practical knowledge of ketamine and major depression. Work exploring ketamine's potential role in the reversal of depression-related synaptic loss shows great promise; however, both the pathophysiology of major depression and the mechanism of ketamine's action remain unconfirmed. In addition, there are a number of outstanding clinical questions: What is the optimal dose and route of administration? How is it possible to sustain the response? What are the long-term side effects of this treatment?

More than 50 clinical trials pertaining to ketamine and depression have been registered to date in the United States. Novel agents with similar glutamatergic properties are also being developed and studied with the hope of comparable benefits and attenuated side-effect profiles. Whether ketamine itself becomes established in general psychiatric practice remains to be seen. Its reported effects, thus far, have nevertheless garnered considerable attention and are catalyzing a paradigm shift in our understanding of, and approach to, major depression.

For background information *see* AFFECTIVE DISORDERS; BRAIN; MENTAL DISORDERS; NERVOUS SYSTEM (VERTEBRATE); NEUROBIOLOGY; NEURON; PHARMACOLOGY; PHARMACY; PSYCHOLOGY; PSYCHOPHARMACOLOGY; PSYCHOSOMATIC DISORDERS; PSYCHOTHERAPY; STRESS (PSYCHOLOGY); SYNAPTIC TRANSMISSION in the McGraw-Hill Encyclopedia of Science & Technology.

John Daniel Cahill

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J. W. Murrough et al., Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression, *Biol. Psychiatry*, 2012.

Key words:

BDNF; depression; ketamine; synaptogenesis

URLs

Drug Fact Sheet: Ketamine

http://www.justice.gov/dea/druginfo/drug_data_sheets/Ketamine.pdf

Major Depression

http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001941

Substances: Ketamine

http://steinhardt.nyu.edu/appsych/chibps/ketamine

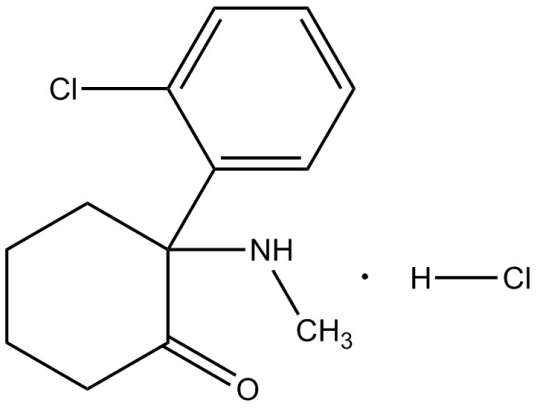
<legend>

Fig. 1. The chemical structure of ketamine hydrochloride [(±)-2-(*o*-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride].

Fig 2. Two-photon microscopic images of rodent neurons after treatment with ketamine (*bottom panel*), showing increased synaptic spine density (*yellow arrows*), as compared to controls (*top panel*). (*Figure courtesy of R. S. Duman and G. K. Aghajanian, Synaptic dysfunction in depression: Potential therapeutic targets, Science, 338(6103):68–72, 2012, DOI:10.1126/science.1222939*)

Fig. 3. The synaptogenic basis of depression and the action of ketamine. See text for more details. LTD, long-term depression. (*Figure courtesy of R. S. Duman and G. K. Aghajanian, Synaptic dysfunction in depression: Potential therapeutic targets, Science, 338(6103):68–72, 2012, DOI:10.1126/science.1222939*)

Figure 1:



Ketamine Hydrochloride

Or

(±)-2-(o-Chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride

Figure 2:

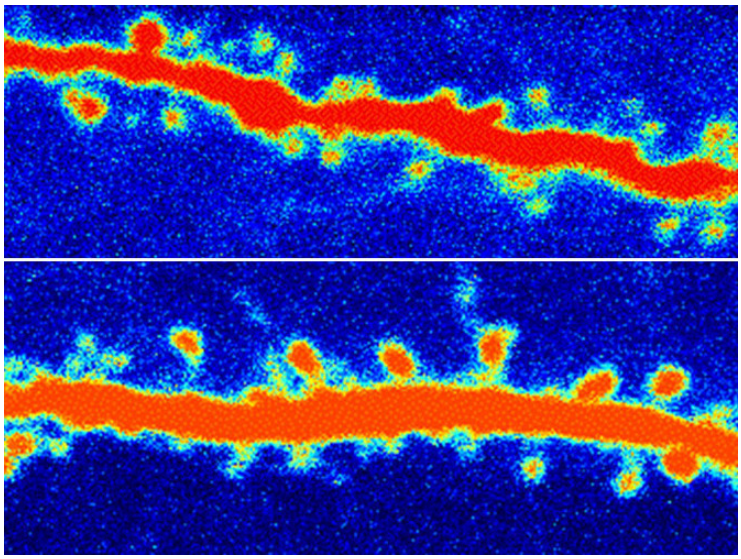
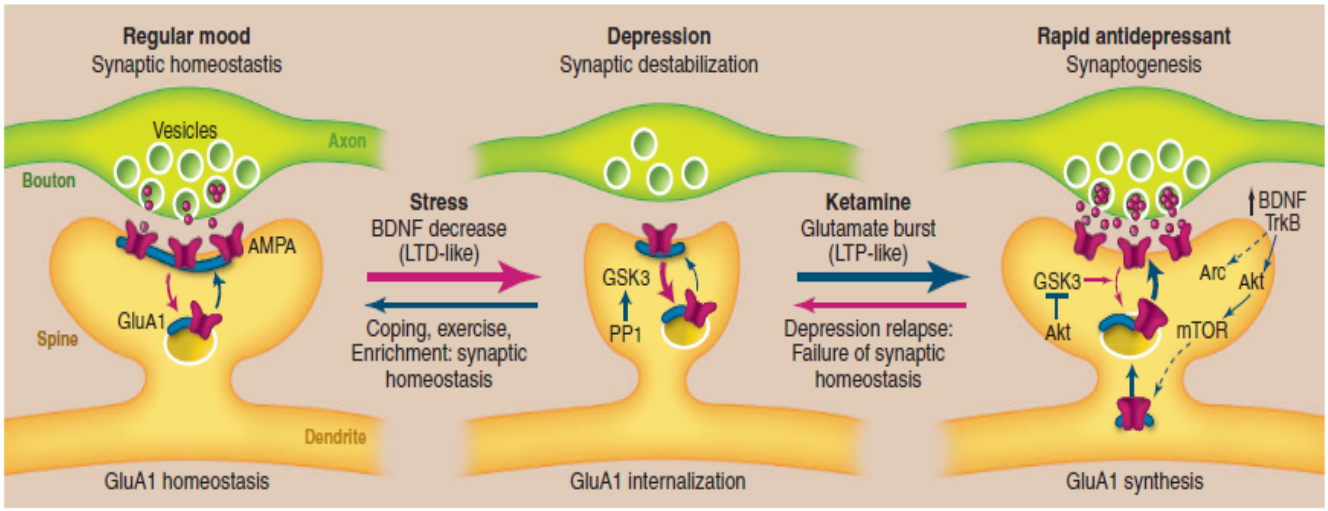


Figure 3:


Regular mood
Synaptic homeostastis
Vesicles
Axon
Bouton
AMPA
GluA1
Spine
Dendrite
GluA1 homeostasis
Stress
BDNF decrease
(LTD-like)
Coping, exercise,
Enrichment: synaptic
homeostasis
Depression
Synaptic destabilization
GSK3
PP1
GluA1 internalization
Ketamine
Glutamate burst
(LTP-like)
Depression relapse:
Failure of synaptic
homeostasis
Rapid antidepressant
Synaptogenesis
BDNF
TrkB
Arc
Akt
GSK3
Akt
mTOR
GluA1 synthesis

SUPPLEMENTARY MATERIAL FOR WORK 3

The Psychosis-Like Effects of Δ^9-THC Are Associated with Increased Cortical 'Noise' in Healthy Humans

Supplemental Information

Supplemental Text

Supplemental Tables

Supplemental Figures

Supplemental References

Subjects, Regulatory Approvals, and General Study Procedures

The study was conducted at the Neurobiological Studies Unit of the VA Connecticut Healthcare System (VACHS; West Haven, CT). Subjects were recruited by advertisements and by word of mouth, and were paid for their participation. The study was approved by the institutional review boards of the VACHS and Yale University School of Medicine and was carried out in accordance with the Helsinki Declaration of 1975. Δ^9-THC was administered with the approval of the U.S. Food and Drug Administration under an Investigational New Drug application (51,671). Subjects were informed about the potential for adverse effects of Δ^9-THC including psychosis, anxiety, panic and abuse liability.

After obtaining written informed consent, subjects underwent a Structured Clinical Interview for DSM-IV (SCID (1)) and were carefully screened for any DSM Axis I lifetime psychiatric or substance use disorder (excluding tobacco and cannabis use) and family history of major Axis I disorder. Subjects were screened at a separate session within about 4 weeks of the first test day. Cannabis-naïve individuals were excluded to minimize any risk of promoting future cannabis use/abuse. Subjects with DSM-IV cannabis dependence based on the SCID were excluded because cannabis dependence has been associated with a blunted response to Δ9-THC (tolerance). The history provided by subjects was confirmed by a telephone interview conducted with a spouse or family member identified by the subject. A general physical and neurological examination, electrocardiogram and laboratory tests (serum electrolytes, liver function tests, complete blood count with differential, urine toxicology and urine pregnancy in women) were also conducted. After screening, subjects were instructed to refrain from alcohol, caffeinated beverages, illicit drugs (other than cannabis) or prescription drugs not approved by the research team for 2 weeks before the study and throughout study participation. Recent users of cannabis, defined as those having used within the last 30 days, were instructed to abstain from smoking for at least 24 hours prior to test day. Test days were rescheduled if subjects reported using cannabis within 24 hours of the test day. Subjects who were not categorized as recent users of cannabis were

reminded not to use cannabis for two weeks before testing and throughout study participation. For this group, abstinence was confirmed by urine drug testing on the morning of each test day.

Electroencephalographic (EEG) Paradigm and Data Acquisition

Multichannel EEGs were recorded from the scalp at a sampling rate of 1000 Hz using a 22 electrode cap (Physiometrix Inc., Billerica, MA, USA) and Neuroscan Synamps amplifiers (Neuroscan SynAmps, Compumedics Neuroscan, Charlotte, NC, USA). Electrode impedances were maintained <10 kΩ and a linked-ear reference was used during the recordings. Vertical and horizontal electro-oculogram (VEOG and HEOG) data were recorded and used for eye-artifact correction.

Subjects sat in an acoustically and electrically shielded booth in front of a computer monitor with eyes open while passively listening to click trains via insert earphones (Etymotic Research, Inc., Elk Grove Village, IL, USA) as part of an auditory oddball task described elsewhere (2). Briefly, the task consisted of a series of frequent 'standard' click trains (20, 30, or 40 Hz), infrequent 'target' tones (1000 Hz), and infrequent task-irrelevant 'novel' distractor sounds presented with a 1250 ms stimulus onset asynchrony in three separate blocks of 180 stimuli each; each block had a different frequency. Standard click trains were 500 ms in duration and 80 dB SPL (C weighting), target tones were 500 ms in duration and 80 dB SPL (C weighting), and novel distractor sounds ranged between 175 and 250 ms in duration and averaged 80 dB SPL (C weighting). The task was programmed in Presentation (Neurobehavioral Systems, Berkeley, CA, USA). Only EEG data preceding each stimulus were included in the analysis described in this paper.

Electroencephalographic Preprocessing

In order to minimize the confounding effects that muscle activity and other sources of artifactual contamination could have on measuring neural noise in EEG signals, raw data were cleaned and only

midline electrodes were used for statistical analyses, given that these electrodes tend to be less contaminated by muscle activity than the rest (3).

Continuous EEG data were band-pass filtered (0.5-100 Hz) with a windowed-sinc finite impulse response (FIR) filter (-6 dB/Hz) (4). To avoid frequency and phase distortions induced by notch filtering, line noise was removed using a multi-tapering technique (5). To clean muscle artifacts, EEG data were decomposed into uncorrelated components using a canonical correlation analysis-based blind source separation (CCA-BSS) algorithm (6). Muscle-related components were identified and removed from the resulting decomposition, and cleaned EEG data were reconstructed using the remaining components. Artifactual components were selected on the basis of their power spectral density (PSD) distribution: the ratio between PSD under and above 15 Hz ($PSD_{<15\mathrm{Hz}}/PSD_{>15\mathrm{Hz}}$) was calculated, and those component having a ratio smaller than 10 were removed (7). This criterion is based on the power law distribution of PSD that has been reported for the human brain ($PSD \propto {}^{1}/_{f^{\alpha}}$ with $\alpha \sim 2$) (8, 9). To better capture and remove different patterns of artifactual activity, a 2-step CCA-BSS-based procedure was used: In the first step, the CCA-BSS algorithm was applied to the complete continuous EEG data, and the resulting artifactual components were removed from the signal; while in the second step, the algorithm was applied independently on non-overlapping 5 trials-length successive signal segments, and the artifactual components of each segment were removed from the corresponding segment only.

VEOG and HEOG channels were used to correct eye movements and blinks artifacts with an exponentially weighted H^{∞} norm-based adaptive filter algorithm (10). Data were segmented in 1150 ms epochs time-locked to stimulus onset, with a 250 ms pre-stimulus segment. Epochs with voltages exceeding a ±100 μV threshold were rejected. The CCA-BSS algorithm was used in addition to the standard voltage-threshold method for artifact removal, given that EEG data free of obvious artifacts may still have an important amount of muscular activity (11, 12). The average number of clean epochs per drug condition used for further analyses was 416.625 (SD = 20.667) for placebo, 420.043 (SD =

11.830) for the 0.015 mg/kg dose, and 419.043 (SD = 13.075) for the 0.03 mg/kg dose. No significant differences were found in the total number of clean epochs between drug conditions (Wald $\chi^2_{(2)}$ = 0.578, p = 0.749). EEG data from midline electrodes (Fz, Cz, and Pz) were selected for analysis given that they tend to be less contaminated by muscle activity (3). Finally, only data from Cz and Fz were used since data from Pz presented artifactual contamination in a number of subjects.

Calculation of Lempel-Ziv Complexity (LZC)

The first step in the calculation of the LZC of a signal is to code the signal into a symbolic sequence. In order to do this, the threshold-crossing approach was chosen given that it is one of the most commonly and successfully used methods for coding signals in fields ranging from pure physics to neuroscience (cf. 13, 14-17). In this method, the range of voltage values of an EEG signal is partitioned in 2 intervals delimited by a threshold T_{Volt}; signal values $\geq T_{Volt}$ are coded as 1, while signal values $< T_{Volt}$ are coded as 0. In this study, the threshold T_{Volt} was chosen to be the median of the signal given that it has been shown to be more representative of the whole signal (in contrast to the midrange) and robust against outliers (in contrast to the mean) than other measures of central tendency frequently used as thresholds (18, 19).

For each subject, electrode and trial, the signal segment preceding the onset of stimulation (-250 to -1 ms) was coded into a binary sequence using the threshold-crossing approach (see described above). The coded signal was then broken into distinct symbolic subsequences or 'words' using Lempel and Ziv's exhaustive parsing algorithm (20). LZC was obtained by dividing (normalizing) the total number of distinct 'words' that were necessary to reconstruct the coded signal by $n/\log_2 n$, the upper bound of the LZC of a symbolic sequence of length n when n tends to infinity (see Figure S1). For each electrode, a single LZC value was obtained by averaging the LZC of the individual trials. Finally, a single LZC value was calculated for each subject by averaging the LZC of the different electrodes.

Statistical Analyses - Relationship between EEG and Behavioral Measures

To characterize the relationship (correlation) between Δ^9-THC induced changes in EEG measures (LZC and signal power) and Positive and Negative Syndrome Scale (PANSS) factors, standardized regression coefficient (βs) were obtained for the longitudinal regression across both Δ^9-THC-active conditions of each PANSS factor score on each EEG measure with a significant main effect of drug (3 for each EEG measure). The resulting standardized regression coefficients were interpreted as correlation coefficients in which a change of 1 standard deviation in the EEG measure x led to a change of β_{xy} standard deviations in the score of the PANSS factor y during acute Δ^9-THC intoxication. For each EEG measure and PANSS factor this was done by fitting a single generalized estimating equations (GEE) model to the data of both Δ^9-THC-active conditions transformed into composite z scores. To preserve the relative differences in the values of each variable between the two Δ^9-THC active conditions, composite z scores were calculated using the mean and standard deviation of the data of both Δ^9-THC-active conditions pooled together. In addition, to obtain the specific relationship between LZC and the PANSS factor scores independently of signal power, the standardized residuals resulting from the regressions of the PANSS factors on signal power (i.e., the part of the variation of the psychosis-like and negative-like behavioral effects that was not explained by signal power) were regressed on the standardized residuals of the regression of LZC on signal power (i.e., the part of the variation of LZC that was independent of signal power) (3 coefficients). No regression was conducted to determine the specific relationship between signal power and the PANSS factor scores independently of LZC, given that no significant main effect of drug on signal power was observed after correcting for LZC (see Methods section). Thus the *p*-values of the resulting regression coefficients were Holm-Bonferroni (HB)-adjusted for 9 comparisons (6 for LZC and 3 for signal power). All the analyses of this section were done in SPSS 21 (IBM Corporation, Armonk, NY, USA).

Effects of Recent (30 Day) Cannabis Exposure

We conducted exploratory analyses examining the differences in the effects of Δ^9-THC on LZC between recent and not-recent users of cannabis. The LZC data from the two Δ^9-THC-active conditions were fitted with a GEE model with an unstructured working correlation matrix. Drug condition (0.015 and 0.03 mg/kg), cannabis use (recent and non-recent users), and an interaction term (drug condition*cannabis use) were included in the model as explanatory variables. As expected, the results showed a significant main effect of drug condition on LZC (Wald $\chi^2_{(1)} = 19.213$, $p < 0.001$), with the 0.03 mg/kg dose inducing higher LZC than the 0.015 mg/kg dose. No significant effects were observed for recent exposure to cannabis and the interaction between drug condition and recent exposure to cannabis (both *ps* > 0.1). These results do not support the hypothesis that recent cannabis exposure affects the effects of Δ^9-THC on LZC.

Plasma Samples of Δ^9-THC and Its Metabolite Δ^9-THC-COOH

Plasma was sampled at several time points from the IV line from the arm opposite to the one used for administering the study drug for determination of 11-nor-Δ^9-THC-9-COOH (Δ^9-THC-COOH) and analyzed using methods previously described (21).

Relationship between P300 and Both LZC and Behavioral Measures

Exploratory analyses were performed in which P3a and P3b peak amplitudes and latencies were regressed on LZC across the three drug conditions using GEE models with unstructured working correlation matrices. Peak P3a and P3b amplitudes and latencies were calculated as described in (2). Significance levels were Holm-Bonferroni adjusted for 4 comparisons. P3a, P3b, and LZC measures were obtained for electrode Cz (Pz was removed during the preprocessing due to artifactual contamination). The results showed a significant inverse relationship between LZC and both P3a (β = -0.391, Wald $\chi^2_{(1)}$ =

16.712, p_{Adj} < 0.001) and P3b (β = -0.419, Wald $\chi^2_{(1)}$ = 10.100, p_{Adj} = 0.002) peak amplitudes. No significant relationships were found between LZC and latencies of the peaks (ps_{Adj} > 0.1).

Event-related potentials (ERPs) have been shown to be sensitive to the acute effects of Δ^9-THC on brain activity (2). However, it is not clear which measure is more sensitive to the pathophysiology of the psychosis-like effects induced by Δ^9-THC. In order to compare the sensitivity of LZC and ERPs, the post-stimulation period of the data used for calculating LZC was used to obtain the peak amplitudes and latencies of the P3a and P3b ERPs at electrode Cz (Pz was excluded from analyses due to artifactual contamination). Specifically, to obtain the ERPs: 1) EEG data was low-pass filtered (30 Hz) with a windowed-sinc FIR filter (-6 dB/Hz) (4), 2) the mean voltage amplitude of the baseline period (-250 to -1 ms) of each trial was substracted from the whole trial, 3) trials were averaged in a point-by-point manner, and 4) the peaks were automatically detected as the highest positive value within the post-stimulation time interval 250-500 ms. Then, psychosis-like behavioral effects (PANSS factor scores) were regressed independently on the peak and amplitude of the ERPs (P3a or P3b) during the Δ^9-THC-active conditions. Each regression was done by fitting a single GEE model with an unstructured working correlation matrix to the data of both Δ^9-THC-active conditions transformed into composite z scores. The *p*-values of the resulting standardized regression coefficients were HB-adjusted for twelve comparisons (2 measures for ERP x 2 ERPs x 3 behavioral-effects).

The analyses revealed that there were no significant coefficients for any of the regressions, either before or after correcting for multiple comparisons (all ps_{Adj} > 0.1). These results suggest that LZC is more sensitive to the pathophysiology underlying the psychosis-like effects of Δ^9-THC than the P3a and P3b ERPs.

Spectral Analysis

In order to obtain the spectral power per frequency band (band power) during the baseline period, for each subject, the signal of each electrode was band-pass filtered (0.5-100 Hz) with a windowed-sinc FIR filter (-6 dB/Hz) (4) with cutoff frequencies corresponding to the traditional frequency bands (δ [1-4 Hz], θ [4-8 Hz], α [8-13 Hz], β [13-30 Hz], $\gamma 1$ [30-55 Hz], $\gamma 2$ [65-100 Hz). Then, for each subject, electrode and frequency band, signal power was obtained by calculating the root-mean-square power (average of the signal's squared amplitude) of each trial's pre-stimulation interval (-250 to -1 ms) and then averaging across trials. Finally, for each subject and frequency band, a single signal power value was obtained by averaging across electrodes.

The effect of drug condition (placebo, 0.015 mg/kg, and 0.03 mg/kg) on band power was assessed using GEEs (22, 23) with unstructured working correlation matrices. Independent GEE models were fitted for each frequency band and *p*-values were adjusted for multiple comparisons (6 comparisons, one per frequency band) with the HB method. Post-hoc pairwise comparisons (3 per model) were performed for those models with a significant main effect of drug condition and the *p*-values were HB-adjusted for the total number of pairwise comparisons performed across all the models (3 per model with a significant main effect of drug condition).

To characterize the relationship between Δ^9-THC-induced changes in band power and psychosis-like behavioral effects, standardized regression coefficient (βs) were obtained for the longitudinal regression of each PANSS factor score on each band power that had a significant main effect of drug condition across both Δ^9-THC-active conditions. *p*-values were HB-adjusted depending on the total number of comparisons (3 per model –one per behavioral measure– with a significant main effect of drug). For each frequency band and PANSS factor, a longitudinal regression was conducted by fitting a single GEE model with an unstructured working correlation matrix to the data of both Δ^9-THC-active conditions transformed into composite z scores. The *p*-values of the resulting regression coefficients

were HB-adjusted for nine comparisons. All the analyses of this section were performed in SPSS 21 (IBM Corporation, Armonk, NY, USA).

The analyses revealed that there was a significant main effect of drug condition on spectral power only for the β-band (Wald $\chi^2_{(2)} = 20.294$, $p_{Adj} < 0.001$; $ps_{Adj} > 0.1$ for the other frequency bands). No significant coefficients (all $p_{Adj} > 0.1$) were found for the regression of the behavioral effects on β-band power for the Δ9-THC-active conditions.

Analysis Comparing Information Contained in Binarized vs. continuous (Non-Binarized) Signals

To obtain an estimate of the information shared by each frequency component of the EEG signals and the binarized full spectrum (0.5-100 Hz) signals used for calculating LZC, we calculated the mutual information (MI) between them. MI refers to the information shared between two signals expressed as an absolute (24). In the calculation of MI, the same information between signals is captured only once. To illustrate this take the two sentences below:

Sentence #1: *Santa Claus is dressed in a red robe*.

Sentence #2: *Santa Claus is dressed in a red robe. Santa Claus is dressed in a red hat. Santa Claus is dressed in red shoes*.

To illustrate this further, assuming that each word represents 1 bit of information, in the calculation of the MI between sentences #1 and #2, the information of the words common to both sentences (highlighted in yellow) is counted only once, even though some words (*Santa, Claus, is, dressed, in, a, red*) are repeated three times in sentence two. The words *hat* and *shoes* (highlighted in green) are identified as the only pieces of information that are not present in both sentences. Thus, the MI between the sentences is calculated as 8 bits (*Santa, Claus, is, dressed, in, a, red, robe*).

In the case of two identical signals, the MI between them (self-MI) is an index of the absolute amount of nonredundant information of each one of the (identical) signals. To illustrate this, take the

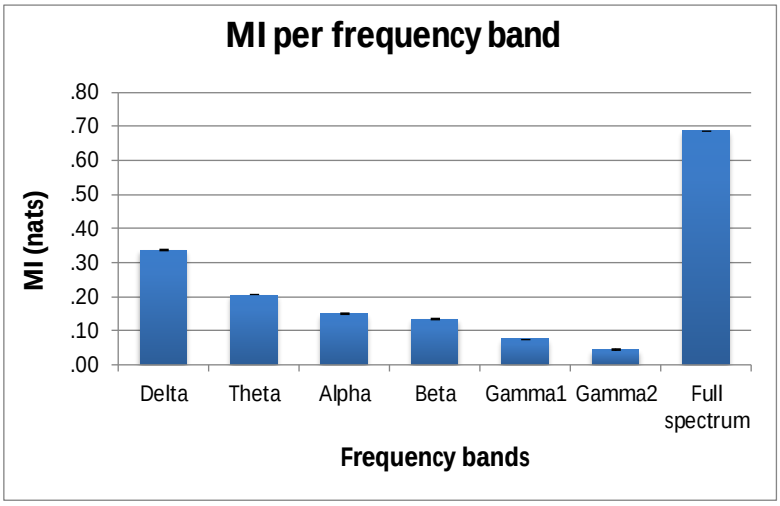
two sentences below:

Sentence #1: *Santa Claus is dressed in a red robe. Santa Claus is dressed in a red hat. Santa Claus is dressed in red shoes.*

Sentence #2: *Santa Claus is dressed in a red robe. Santa Claus is dressed in a red hat. Santa Claus is dressed in red shoes.*

Assuming that each word represents 1 bit of information, there are 10 bits of nonredundant information in each sentence (*Santa, Claus, is, dressed, in, a, red, robe, hat, shoes*).

In order to calculate MI in our data, full-spectrum (0.5-100 Hz) EEG signals from electrodes Fz and Cz were bandpass-filtered to obtain the frequency components corresponding to the traditional frequency bands (delta [1-4 Hz], theta [4-8 Hz], alpha [8-13 Hz], beta [13-30 Hz], gamma1 [30-55 Hz], gamma2 [65-100 Hz]). For each subject, electrode, and trial (see the Methods section), the frequency components of the baseline period (-250 ms to -1 ms) were obtained, and the MI between each frequency component and the binary signal used for calculating LZC (full-spectrum [0.5-100 Hz] EEG signal binarized with the threshold (median)-crossing approach) was calculated. Finally, for each frequency component, MI was averaged across trials and then across electrodes in order to obtain a single MI per subject for each frequency component.



MI data were fitted with a GEE model with an unstructured working correlation matrix, and with frequency band as factor. Pairwise comparisons were performed and *p*-values were adjusted with the HB method for 21 comparisons. The results showed a significant effect of

frequency band on MI (Wald $\chi^2_{(5)} = 30358.481$, $p_{Adj} < 0.001$). Post-hoc analyses revealed that all pairwise comparisons were significant (all $ps_{Adj} \leq 0.001$) and that from largest to smallest, MI per frequency band can be sorted in the following way (adjoining figure): delta > theta > alpha > beta > gamma1 > gamma2.

Table S1. Schedule of procedures

Time	Procedure	Procedure
~4 weeks before test day	· Medical and psychiatric history, SCID, cannabis/drug/alcohol use, confirmation of history with collateral	· Chemistry, hematology, urine toxicology, urine pregnancy, EKG, vital signs, height and weight
-120 (~8 am)	· Is subject NPO after midnight? · Last use of alcohol · Last use of tobacco · Check for recent stressors: No/Yes (specify)	· Last use of THC · Last use of caffeine · Any meds in the past week? No/Yes (specify)
-90 (8:30 am)	· Send urine tox: Positive/Negative · Urine pregnancy test (female) · Vital signs: BP (sitting); Pulse	· Breathalyzer · Insert IV lines · Standard light breakfast
-60 (9 am)	· PANSS	· Vital signs: BP (sitting); Pulse
-30 (9:30 am)	· EEG recording	
-5 (9:55 am)	· Vital signs: BP (sitting); Pulse	· Blood sampling for THC/THC-COOH
0 (10 am)	IV THC (0.0015 mg/kg, 0.015 mg/kg or 0.03 mg/kg) or Placebo over 10 minutes.	
+5 (10:05 am)	· Vital signs: BP (sitting); Pulse	
+10 (10:10 am)	· Blood sampling for THC/THC-COOH · Vital signs: BP (sitting); Pulse · End of THC infusion	· PANSS
+30 (10:30 am)	· ERP recording	· Vital signs: BP (Sitting); Pulse
+80 (11:20 am)	· Vital signs: BP (sitting); Pulse · PANSS	· Blood sampling for THC/THC-COOH
+240 (2 pm)	· Vital signs: BP (sitting); Pulse	· Blood sampling for THC/THC-COOH

End of Test Day	· Safety Checklist:
	  · MMSE (nursing)
	  · Field sobriety test
	  · Exit interview
		· Discharge instructions

Safety Follow up: 1 and 3 months after last test day for cannabis use, psychiatric symptoms		

BP, blood pressure; EEG, electroencephalogram; EKG, electrocardiogram; ERP, event-related potential; MMSE, Mini-Mental State Examination; NPO, nil per os; PANSS, Positive and Negative Syndrome Scale.

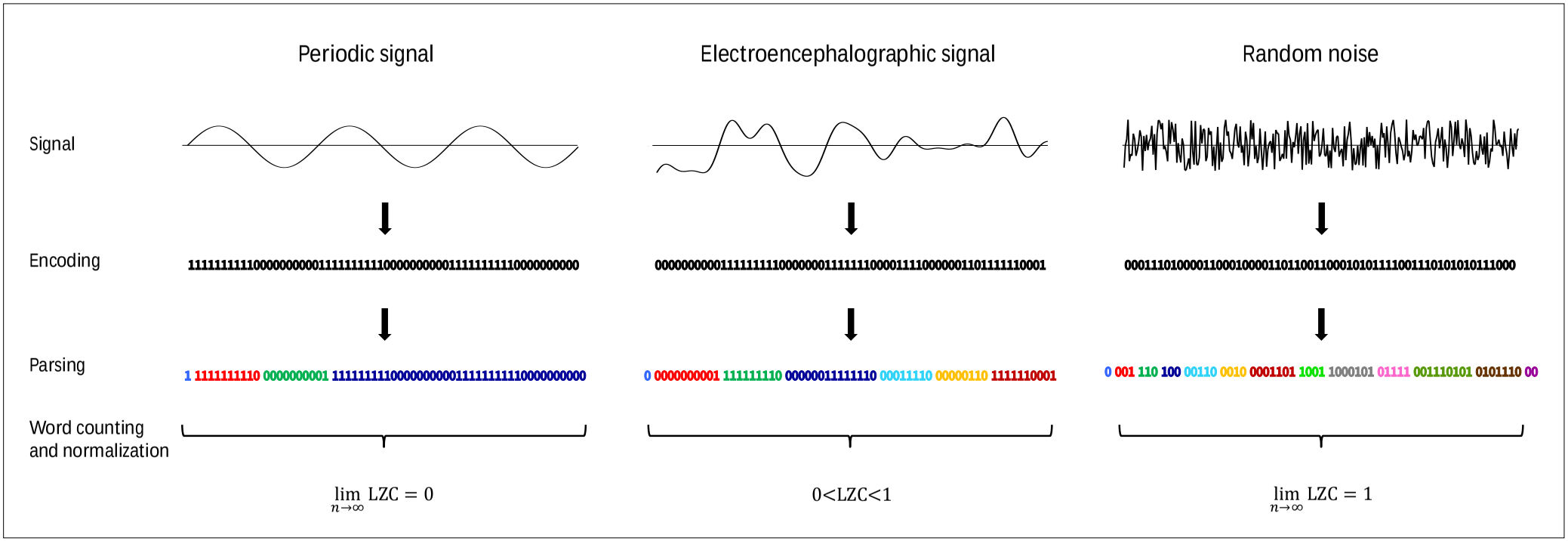


Figure S1. Lempel-Ziv complexity in recurrent, electroencephalographic, and random signals. The figure shows the steps followed to calculate Lempel-Ziv complexity (LZC) in three different types of signals: periodic (regular), electroencephalographic, and white noise. From top to bottom, the first step consists of coding the signal into a binary (1 s and 0 s) symbolic sequence; then the sequence is parsed in order to obtain the distinct symbolic subsequences or 'words' forming it (for each type of signal, different words are shown as different color sequences separated by dots); finally, the number of distinct words is determined and the result normalized to obtain an LZC value that approaches 0 for a regular sequence and 1 for a random sequence when the length of the signal (n) tends to infinity. Note that the number of distinct words is minimal for the periodic signal and maximal for random noise, while the number of words of the electroencephalographic signal lies between both extremes.

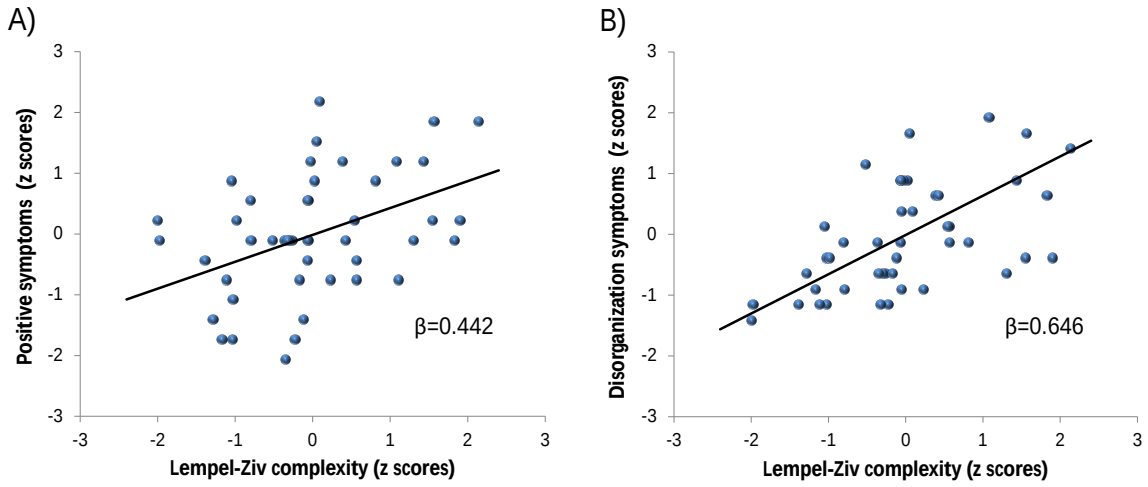


Figure S2. Δ^9-THC-induced positive and disorganization symptoms versus Lempel-Ziv complexity uncorrected for signal power. The figure shows the linear regression lines and standardized coefficients of the positive (**A**) and disorganization (**B**) symptoms factors of the PANSS on Lempel-Ziv complexity (LZC) uncorrected for signal power. PANSS scores and LZC values are presented in z scores.

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