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The neural basis of aberrant salience
attribution in unmedicated patients with
schizophrenia spectrum disorders

Author

Carl Delfin

Supervisor

Jimmy Jensen

Examiner

Marcus Johansson

Abstract

Due to abnormal functioning of the brain's reward and prediction system patients with schizophrenia spectrum disorders are thought to assign salience to non-relevant objects and events and to form context-inappropriate associations. The brain's ventral striatum is critical in the formation of associations, and aberrant associations are believed to create delusional content during psychosis. The study wanted to examine the neural response, particularly in the ventral striatum, combined with subjective reports as patients learn associations in an aversive Pavlovian conditioning paradigm. The stimuli were randomized and involved circles of different colors. The conditioned stimuli (CS+) was followed by an unconditioned stimuli (US), consisting of an unpleasant sound, in 50% of events. The unconditioned (CS-) stimuli was followed by a low, not unpleasant sound in 50% of events. The degree of striatal activation was thought to be associated with the severity of patient's illness. Functional magnetic resonance imaging (fMRI) blood-oxygen-level dependent (BOLD) responses were examined in eleven unmedicated non-institutionalized patients with schizophrenia spectrum disorders and 15 matched healthy controls. No significant within group differences in neural or subjective response to the [CS+ > CS-] contrast were found. No significant associations between severity of illness and degree of striatal activation in response to CS+ or CS- were found. Significant differences in neural activation for the [CS+ > CS-] contrast were found in the ventral striatum, the right inferior frontal gyrus, and the right angular gyrus, with patients exhibiting stronger activation compared to controls. The results and implications are discussed along with suggestions for future research.

The schizophrenia spectrum is a collection of common and severe neuropsychiatric disorders found in every society and every culture in the world (Barbato, 1998). It is an elusive phenomenon and remains one of the most mysterious disorders, a major therapeutic challenge, and one of the last frontiers of brain research (Seeman & Kapur, 2000).

Etymologically the word 'schizophrenia' is a concatenation of the greek words *schizo*, meaning split, and *phren*, meaning mind. The word originates from Eugen Bleulers (1857-1939) revision of Emil Kraepelins (1856-1926) concept 'dementia praecox', and serves to illustrate the severe fragmentation of thinking and personality the disorder instills in its victims (Andreasen, 1995). No single pathognomonic symptom of schizophrenia exists. Diagnosing according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, "involves the recognition of a constellation of signs and symptoms associated with impaired occupational and social functioning" (DSM-5; American Psychiatric Association, 2013, p. 100). These symptoms are generally divided into positive (e.g., hallucinations, delusions, or disorganised speech) and negative (e.g., alogia, anhedonia or avolition), with positive symptoms usually being the ones prompting clinical attention. Notwithstanding the complexity of the disorder, diagnostic reliability is high and stands on very solid ground. A skilled clinician is usually able to recognize the classic signs and symptoms, despite language barriers or when full interviews are unattainable (Andreasen, 1995).

While incidence rates for schizophrenia are relatively low — a review based on a total of 1 721 prevalence estimates from 46 countries and found a median lifetime risk of 4 per 1000 persons (Saha, Chant, Welham, & McGrath, 2005) — the condition leads to substantial burden, both for the affected individual and for society at large. For individuals, the disorder is usually chronic and while some patients do well, most are incapacitated to the degree that they require medications for the rest of their lives (Andreasen, 1995). Schizophrenia affects social functioning such as occupational performance, self-care and relationships, both within the family and in a wider social context (Barbato, 1998). The age of onset is relatively low, usually late teens or early twenties, and those affected often feel as if they have lost their identity, autonomy, and mental capacity (Andreasen, 1995), which might help explain why schizophrenia leads to higher mortality rates and a lifetime risk of suicide estimated at above 10% (Barbato, 1998). For society, the direct costs of schizophrenia (i.e., the costs of providing care to affected individuals) range between 1.6% and 2.6% of total healthcare expenditures in western countries (Barbato, 1998). In Sweden, the societal costs of schizophrenia amount to around 15 billion SEK per year (Svenska Psykiatriska Föreningen, 2009).

The disorder has a proven and substantial genetic origin — heritability estimates have ranged from 63% to 83% (Kendler & Diehl, 1993; Cannon, Kaprio, Lönnqvist, Huttunen, & Koskenvuo, 1998) — and a polygenic mode of inheritance (i.e., its phenotypic characteristics are attributable to several genes). Still, the genetic etiology of schizophrenia remains elusive. Studies have shown epistasis between various genes linked to schizophrenia, although the functional relevance of these genes remain

unexplained (Prasad et al., 2002; Talkowski et al., 2008). In addition to schizophrenia's genetic etiology, environmental risk factors are also emphasized (Howes & Kapur, 2009). Prominent ones, as reviewed by Cantor-Graae (2007), include immigration, urban upbringing, substance abuse, lower levels of socioeconomic status and higher levels of social adversity (e.g., parental unemployment, single-parent household, welfare-dependant household). These factors operate on different levels ranging from societal to family-individual, and may interact with each other in different and not always apparent ways. As genetic and environmental factors are entangled rather than isolated from each other, integration of both biological and social perspectives is suggested for preventive measures (Cantor-Graae, 2007; Howes & Kapur, 2009).

Irrespective of its etiology, the concept of schizophrenia has since its first inception over a hundred years ago been envisioned as an organic brain disease (Shenton, Dickey, Frumin, & McCarley, 2001). Despite this, initial research into the neuropathology of schizophrenia offered few conclusive answers and was soon abandoned in favour of psychoanalysis and social psychiatry (Ron & Harvey, 1990). The lack of progress was characteristically noted by Plum (1972) who claimed that "schizophrenia is the graveyard of neuropathologists". Fortunately, technological advancements in neuroimaging during the latter part of the 1970s reinvigorated interest in the neurological underpinnings of the disorder (Shenton et al., 2001). Following this resurgence, Ron and Harvey (1990, p. 725) proclaimed that "to have forgotten that schizophrenia is a brain disease will go down as one of the great aberrations of twentieth century medicine." Consequently, most current research into schizophrenia is focused on identifying its pathophysiology, trying to link symptoms to their inherent neural mechanisms (Andreasen, 1995).

As our knowledge about the neuropathophysiology of schizophrenia advances, both preventive measures and treatment should help improve the lives of those who suffer under the burden of schizophrenia. The current study hopes to contribute by investigating the neural underpinnings of aberrant salience attribution, which is thought to serve as the origin of psychotic delusions.

Schizophrenia, Psychosis and Delusions

While there are many symptoms, both positive and negative, the hallmark of schizophrenia is psychosis (Kapur, 2003). A key feature of psychosis is delusions; distortions in the perception of reality, defined as "fixed beliefs that are not amenable to change in light of conflicting evidence" (American Psychiatric Association, 2013, p. 87). Delusions come in different thematic varieties, such as persecutory (i.e., belief that one is at risk of harm or harassment by an individual, group or organization), grandiose (i.e., belief that one possesses exceptional abilities) or somatic (i.e., beliefs regarding one's health).

A precise phenomenological definition of what 'beliefs' actually are is notoriously difficult to achieve (Dennett, 1995). If adapting a reductionistic approach (Corlett,

Taylor, Wang, Fletcher, & Krystal, 2010), beliefs may be defined as what help us organize existing information and coordinate adaptive responses; past experiences that are utilized to predict the future. As such, beliefs are theorized to be the result of learned associations between sensory stimuli and salient events (Dickinson, 2001), where highly salient stimuli that systematically predict important consequences receive more attention (Mackintosh, 1975). It has been proposed that when an event occurs that corresponds to our expectancies, it will amplify its representation in short-term memory and subsequently increase the strength and likelihood of being incorporated into long-term memory. When the opposite happens — when an event violates expectancy — the short-term memory is reset and an orienting response activated, permitting the acquisition of new explanatory associations (Grossberg, 1982).

On a neural level, beliefs are thought to be represented through the formation and strengthening of synaptic connections (Corlett et al., 2010). However, prior beliefs also have a strong influence on sensory inputs, trying to conform them to our expectations. Results from Bayesian neural networking models of the visual cortex have shown that neural networks learn statistical regularities of the natural world, and that each level in the hierarchical network tries to predict responses at the following lower level via feedback connections. The residual error of this prediction and the actual response is sent back upwards through feedforward connections, attempting to correct the input signal at each level (Rao & Ballard, 1999).

Similarly, according to a learning framework developed by Friston (2005), the brain employs hierarchical models to construct dynamic and context-sensitive Bayesian prior expectations. In the framework, learning emerges from synaptic efficacy in an effort to minimize the brain's free energy, as defined by statistical physics, which according to Friston (2005) is essentially similar to the notion of the brain trying to minimize surprise about sensory inputs. Delusional beliefs thus may be explained as a disruption of the brain's normal Bayesian prediction mechanisms. Several studies have demonstrated prediction errors in patients suffering from schizophrenia (e.g., Gradin et al., 2011; Krawitz, Braver, Barch, & Brown, 2011; Moran, Rouse, Cross, Corcoran, & Schürmann, 2012; Dowd & Barch, 2012; Yamashita & Tani, 2012; Neuhaus, Brandt, Goldberg, Bates, & Malhotra, 2013), and such errors lead to a mismatch with expectancies between predictable and irrelevant events.

The idea of prior beliefs shaping sensory inputs originally stems from the concept of 'unconscious inferences' (von Helmholtz, 1866), and is perhaps best evidenced by the hollow mask optical illusion, where a concave face such as a hollow mask is perceived as a normal convex face (Gregory, 1997). Interestingly, schizophrenia patients have shown less susceptibility to optical illusions compared to healthy controls, presumably due to a strengthening of bottom-up processes and reduced synaptic efficacy of top-down connections (Dima et al., 2009). This would suggest that schizophrenic patients are less able to utilize top-down strategies during perception, instead relying on stimulus-driven processing.

Endogenous psychosis evolves slowly, in a process during which the affected individual experiences a sense of heightened awareness and attention in a world that may seem changing, strange and sinister (Corlett et al., 2010; Kapur, 2003). Due to the failure of prediction mechanisms and reliance on stimulus-driven processing, what is a contextually driven process in healthy individuals instead becomes an aberrant attribution of salience to non-relevant external objects and internal representations. This results in delusional misrepresentations, and indeed, aberrant salience attribution is a well established result in schizophrenia research (e.g., Jensen et al., 2008; Roiser et al., 2009; Diaconescu et al., 2011; Walter et al., 2010; Roiser, Howes, Chaddock, Joyce, & McGuire, 2013).

Because of the unstable and strange experience these aberrant salience assignments evoke, higher-level non-sensory circuits in the brain are called upon to draw inferences and encode beliefs (Schmack et al., 2013). Ergo, delusions may be elucidated as bottom-up processing of random, abnormally salient objects and events, followed by the individual's own higher-level, non-sensory cognitive explanations, acting as a relief effort to make sense of and bring consistency to the constantly changing world. Since the delusional content according to the aberrant salience theory is individually constructed, the theory also explains why there are variations in the phenomenological expression of the disease; the delusions are embedded in a cultural context and are permeated by psychodynamic themes relevant to the individual (Kapur, 2003).

Delusions and Dopamine

The role of dopamine in trying to understand the pathophysiology of psychosis has been one of the most enduring ideas in the field (Howes & Kapur, 2009), much due to the fortuitous discovery of chlorpromazine (Charpentier, Gailliot, Jacob, Gaudechon, & Buisson, 1952) — the world's very first antipsychotic — and its subsequent introduction into clinical psychiatry (Laborit, Huguenard, & Alluaume, 1952). The most recent advancement of the dopamine theory of schizophrenia comes from Howes and Kapur (2009), who propose that changes in multiple underlying transmitter and neural systems lead to excessive, chaotic and context-inappropriate dopamine release, or hyperdopaminergia, in an area of the brain known as the striatum.

Increased striatal dopamine transmission has been observed in both prodromal and psychotic states in schizophrenia patients (Howes et al., 2007; Kegeles et al., 2010). Furthermore a recent study provided the first evidence that intrinsic activity in the striatum corresponds to both disorder states and symptom dimensions in schizophrenia (Sorg et al., 2013). In addition, results from animal studies have shown that activity in the striatum is linked to high intensity visual and auditory events (Horvitz, Stewart, & Jacobs, 1997), as well as both novel (Legault & Wise, 2001) and aversive (Young, 2004) stimuli. Furthermore, the degree of salience has been positively correlated with the degree of striatal activation in healthy human subjects (Zink, Pagnoni, Chappelow, Martin-Skurski, & Berns, 2006).

It is suggested that delusional beliefs are formed neurochemically due to hyperdopaminergia leading to noisy striatal signaling and disruptions in the brain's reward and prediction systems, with the end result of merely coincident events appearing as highly salient (Kapur, 2003). Well-predicted events have been shown to elicit the same ventral (i.e., lower) striatal activation for schizophrenia patients that surprising events do for healthy subjects, which asserts the role of the striatum as a key node of dysfunction in the neural circuitry of schizophrenia patients (Morris et al., 2012). The ventral striatum is known as the limbic-motor interface, serving as a nexus for limbic and cortical brain regions and integrator for the cognitive and affective processes that influence motor output (Pujara & Koenigs, 2014). As such, the ventral striatum is thought to serve as the brain's connection between relevant stimuli and adaptive behaviours, facilitated by dopamine transmission (Ferré, 1997). Hence, when striatal dopaminergic transmissions are chaotic and context-inappropriate, salience is misattributed to neutral stimuli.

The striatum contains the highest concentration of dopamine receptors in the brain (Björklund & Lindvall, 1984), and while it is not known exactly what causes hyperdopaminergia, increased striatal dopaminergic turnover is one of the best established results in schizophrenia research (Miyake, Thompson, Skinbjerg, & Abi-Dargham, 2010). It is believed to be the final common pathway leading to positive psychotic symptoms (Howes & Kapur, 2009), such as aberrant salience and delusional beliefs.

Aberrant Salience Attribution

While delusional beliefs *per se* may be difficult to investigate on a neural level, the formation of simple yet aberrant associations is experimentally more feasible to examine.

Studies using Pavlovian conditioning and healthy volunteers have shown that the ventral striatum bears a significant role in learning both appetitive and aversive associations (e.g., McClure, Berns, & Montague, 2003; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003; O'Doherty et al., 2004; Jensen et al., 2007). In healthy subjects, processing of conditioned stimuli is enhanced relative to processing of neutral stimuli, while in schizophrenia neutral stimuli are rendered abnormally relevant, which might explain how aberrant associations are formed (Balog, Somlai, & Keri, 2013). For instance, Diaconescu et al. (2011) found that schizophrenia patients could not subjectively distinguish between conditioned and neutral stimuli, and that patients showed increased striatal activity to the neutral stimuli compared to the conditioned stimuli. Healthy controls reflected an opposite pattern and showed increased neural activity to the conditioned stimuli compared to the neutral stimuli, suggesting that patients processed the neutral stimuli as motivationally salient, just as how controls processed the conditioned stimuli to be predictive of reward.

Furthermore, studies have also shown how striatal activity may predict symptom severity. The severity of negative symptoms has been related to increased aberrant ventral striatal activity in schizophrenia patients (Juckel et al., 2006a, Juckel et al.,

2006b; Simon et al., 2010; Morris et al., 2012; Sorg et al., 2013). In addition, the severity of positive symptoms has been related to synchronous activity of the dorsal striatum (Sorg et al., 2013), and increased striatal activation in schizophrenia patients has been correlated with higher total symptom scores during expected reward conditioning (Morris et al., 2010).

Treatment of psychosis involves antipsychotic medicine. All currently licensed antipsychotic drugs block striatal dopamine D₂ receptors (Talbot & Laurelle, 2002) and suppress BOLD (blood-oxygen-level dependent, see p. 12) activity related to instrumental reward learning (Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006) and aversive conditioning (Menon et al., 2007). Although previous studies have investigated the neural correlates of aberrant learning and salience coding, several authors (e.g., Jensen et al., 2008; Roiser et al., 2009; Walter et al., 2010) have called for replication using unmedicated subjects.

To the authors knowledge, only a few studies utilizing conditioning paradigms have included unmedicated patients in schizophrenia research. A study investigating the brain reward system in a monetary delay task found that unmedicated schizophrenia patients showed reduced striatal activation when reward-indicating cues were presented, compared to healthy controls (Juckel et al., 2006b). The result has been further corroborated in a monetary reward task, with unmedicated first episode schizophrenia patients showing reduced right ventral striatal activation during reward anticipation, and with more pronounced hypoactivation corresponding to more salience being attributed to neutral stimuli (Esslinger et al., 2012). A longitudinally designed study also employing a monetary reward task produced similar results, where unmedicated schizophrenia patients at baseline showed decreased activation in the ventral striatum during reward anticipation, as compared to healthy controls. After six weeks of treatment with amisulpride (an antipsychotic dopamine D₂/D₃ receptor antagonist) patients showed an increase in the anticipation related BOLD signal, and were no longer statistically distinguishable from controls (Nielsen et al., 2012). Finally, a recent study showed reduced activation in the ventral striatum during a reward related reversal learning task in unmedicated schizophrenia patients (Schlagenhauf et al., 2014).

It seems that reward anticipation and reward related learning correspond to reduced striatal activation, and that neutral stimuli evoke enhanced striatal activation in unmedicated schizophrenia patients. However, it has yet to be investigated how abnormal associations are formed in unmedicated schizophrenia patients using aversive conditioning. The role of the ventral striatum in processing aversive events has been controversial, but it has been shown that mere anticipation of aversive stimuli directly activates the ventral striatum in healthy human subjects (Jensen et al., 2003). Aversive conditioning also has a major advantage over other paradigms, such as monetary tasks, since aversive stimuli in the form of loud environmental sounds is more realistic and more closely related to the risk factors and stress associated with psychosis (Balog, Somlai, & Kéri, 2013).

In a Pavlovian aversive conditioning paradigm, Jensen et al. (2008) found that when exposed to the neutral stimuli, medicated schizophrenia patients showed a significant activation in the ventral striatum compared to controls. The finding was accompanied with subjective self-reports and physiological galvanic skin conductance results which indicated that schizophrenia patients failed to distinguish between conditioned and neutral stimuli.

AIMS OF THE STUDY

The current study wanted to investigate how aberrant salience attributions are formed in unmedicated schizophrenia spectrum patients, using an aversive Pavlovian conditioning combined with BOLD fMRI and subjective reports. It was hypothesized that patients would show patterns of abnormal learning, both subjectively through self-reports and neurally through either decreased striatal activation in response to the conditioned aversive stimuli, or increased striatal activation in response to the neutral stimuli. Furthermore it was hypothesized that the severity of patient's illness would be correlated with the degree of striatal activation.

METHODS

Subjects

Thirteen patients with schizophrenia spectrum disorders and 15 healthy controls participated in the study. Subjects were recruited between September 2009 and January 2012. Patients were recruited from non-institutional care through clinical staff that were informed about the project. In following with the guidelines of the Regional Ethics Committee, all subjects were advised about the study and gave informed consent. All subjects confirmed that they had understood the task after completion of the experiment, and received payment for their participation. Overall exclusion criteria were previous head injury, neurological disorder, IQ < 70, and age outside the range 18-65 years. Specific exclusion criteria for controls were drug use within the last 12 months, any current psychiatric disorder, or other medical problems thought to interfere with brain function. Patients had not been administered antipsychotics for at least two months. One patient was discarded due to poor image quality. One patient gave informed consent but did not follow through with the experiment. The final cohort consisted of eleven patients and 15 healthy controls (see Table 1).

Patient's diagnosis was based on DSM-IV Axis I disorder and assessed by trained psychiatrists and clinical psychologists. The sample included one patient with unspecified psychosis, one patient with paranoid schizophrenia, one patient with schizoaffective disorder, two patients with delusional disorder, two patients with schizophrenia, and four patients with schizophreniform disorder. Patient's current pos-

itive, negative and general symptoms were assessed through structured clinical interviews immediately before the experiment began, using the Positive and Negative Syndrome Scale (SCI-PANSS; Kay, Fiszbein, & Opfer, 1987). The 30-item instrument consists of three subscales; positive (7 items), negative (7 items) and general (16 items), where each item is rated on a 7-point scale representing increasing levels of psychopathology, ranging from 1 = absent to 7 = extreme. Furthermore a total score is calculated from all item scores. Scoring is done by summing ratings across items, thus possible ranges are 7-49 for the positive and negative scales, 16-112 for the general scale and 30-210 for the total score. The PANSS instrument reliability was measured using Cronbach's α , with $\alpha = .78$ for the positive scale, $\alpha = .84$ for the negative scale, $\alpha = .78$ for the general scale, and $\alpha = .89$ for the total score. (Due to zero variance, one item in the negative scale and one item in the general scale were discarded in reliability analyses.) To ensure that patients and controls were adequately matched, the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997) was administered. Due to missing data only the Information subscale, which evaluates non-academic information individuals are likely to have acquired in our culture, was included in the study. The subscale consists of 28 questions where each correct answer yields one point, for a maximum score of 28.

Table 1. Demographics and clinical data (Mean \pm SD)

	Patients (N = 11)	Controls (N = 15)	Statistic
Sex, no. of females (%)	4 (36)	5 (33)	$\chi^2 = .03^a$
Handedness, no. of right handed ¹ (%)	8 (100)	12 (80)	$\chi^2 = 1.84^a$
Age (years)	29.36 \pm 11.64	27.27 \pm 4.99	U = 79.00 ^a
WAIS-III Information ²	22.43 \pm 4.61	23.87 \pm 3.23	t = .85 ^a
Duration of illness (years)	3.59 \pm 4.11		
PANSS Total score	47.55 \pm 12.52		
PANSS Positive	12.09 \pm 4.55		
PANSS Negative	9.55 \pm 3.21		
PANSS General	25.00 \pm 7.23		

¹ Missing three patients. ² Missing four patients. ^a No significant difference between patients and healthy controls.

Experimental Protocol

In order to study the formation of aberrant associations, fMRI BOLD responses were examined in a classical passive Pavlovian learning paradigm. The conditioned stimuli (CS+) consisted of a colored circle displayed for 2.5 s, which predicted the aversive unconditioned stimuli (US) according to a 50% partial reinforcement schedule. The US consisted of an 800 ms long fire-truck horn burst, the intensity of which was individually adjusted to be "unpleasant but tolerable". Neutral comparators (CS-) consisted of a circle of another color and were followed by a low, not unpleasant tone in 50% of the events. The trials were randomized and consisted of 20 CS+ paired with the US, 20 CS+ unpaired, 20 CS- paired with the low, not unpleasant

tone, and 20 CS- unpaired. Intertrial interval ranged from 9.1 to 10.9 s ($M = 10$ s), during which a fixation cross was displayed. The experimental sessions lasted an average of 16 minutes.

Apparatus

Stimuli presentation and control was facilitated by E-prime software (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Visual and auditory stimuli were presented using VisualSystem and AudioSystem (NeuroNordicLab, Bergen, Norway), respectively, while subjects' responses were recorded using ResponseGrip (NeuroNordicLab, Bergen, Norway).

Functional Magnetic Resonance Imaging

Since aberrant salience attribution is thought to originate from neurostructural and neurofunctional deviations, some kind of instrument is required in order to measure neural activity. There are several non-invasive, *in vivo* techniques available for neuroimaging. Thirty years ago, one of the first imaging studies of schizophrenia used magnetic resonance imaging, MRI, to measure neural activity (Smith et al., 1984). Since then, computed tomography (CT), positron emission tomography (PET), single photon emission CT (SPECT), and functional MRI (fMRI) have all been employed in schizophrenia research (Ahmed, Buckley, & Hanna, 2013).

While each of these techniques have their respective merits and provide a unique perspective on brain function (Lindquist, 2008), the dominant technique for the study of brain function is — and has been for quite some time — fMRI (Voos & Pelphrey, 2013). With an unprecedented increase in use during the last decade and with over 1 500 articles per year reporting fMRI results in 2010 (Nair, 2005; Smith, 2012), the technique affords several advantages, such as lack of ionizing radiation, direct correlation with anatomical imaging, repeatability, and affordability (Gur & Gur, 2010). Functional MRI has evolved to become perhaps the most powerful method available for mapping neural activity in the human brain (Howseman & Bowtell, 1999), and its excellent spatial resolution enables the researcher to visualize neuroanatomical structures involved in complex information processing (Voos & Pelphrey, 2013), such as those involved in aberrant salience attribution. In short, fMRI allows the researcher to make inferences about changes in brain activity that occur as a response to stimulus presentation or task performance.

Unfortunately, how fMRI works is fairly complicated. An introduction to the underlying concepts should enable the reader to fully appreciate the technique as it appears in the following sections. Concepts in *italics* are particularly important.

Nuclear Magnetic Resonance

While an inherently quantum mechanical phenomenon, nuclear magnetic resonance (NMR) may — at least for current purposes — be adequately explained using classical mechanical analogues. In nearly all fMRI studies the MR signal arises from hydrogen nuclei, ^1H , which consist of a single proton (Brown, Perthen, Liu, & Buxton, 2007). The proton has an intrinsic property of angular momentum called spin (see Griffiths & Harris, 1995). Spin in this context is purely quantum mechanical, though a satisfactory analogue would be Earth's spin around its own axis. Since protons are positively charged, the spin generates an electrical current on the proton's surface. In turn, the electrical current creates a small magnetic field, whose strength (or rotational force; torque) is called the magnetic moment. Furthermore, since the proton has mass, its spin results in angular momentum. Together, magnetic moment and angular momentum result in the NMR property. If a nucleus does not have this property, it cannot be used for MRI. A collection of spatially oriented nuclei with the NMR property is called a spin system.

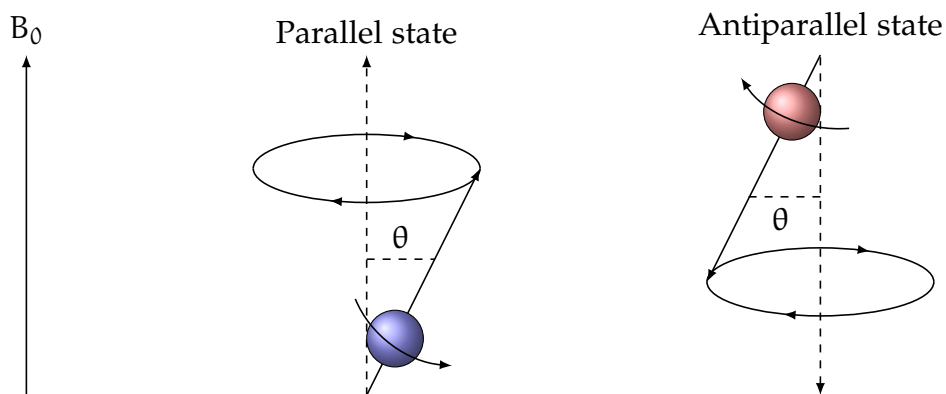


Figure 1. Protons in parallel (low energy) and antiparallel (high energy) states.

In the absence of an external magnetic field the spin axis of protons in free space will be randomly aligned, and the sum of all magnetic moments in a spin system, the net magnetization, will be zero. When introduced to an external magnetic field B_0 , the protons will spin either up or down. By convention, spin up is referred to as parallel to the direction of B_0 , and vice versa (see Figure 1). The proton will precess around the direction of the B_0 at an angle θ and with an angular frequency of known as the Larmor frequency — determined by the strength of B_0 — but will do so at a random phase. In a process called *excitation*, radiofrequency (RF) coils within the MRI scanner send out electromagnetic waves (i.e., photons) corresponding to the Larmor frequency, which cause low energy protons to switch state. After a while the spin system reaches a point where there is an equal number of spins in each state, thus establishing a transverse magnetization and phase coherence (Huettel, Song, & McCarthy, 2009). When excitation stops the spin system will seek to return to its original thermal equilibrium, thus releasing the absorbed energy in the form of photons of the same frequency as the energy difference in spin levels (i.e., the Larmor frequency) in a process called *relaxation*. These photons are received by the RF coil,

and the change in current in the RF coil between excitation and relaxation constitute the raw MR signal.

The relaxation mechanism operates on two levels; loss of spin phase coherence, called T_2 decay, and high energy state protons returning to their pre-excitation low energy state, called T_1 recovery. Typically, T_1 is measured in seconds and T_2 is measured in milliseconds. Both vary depending on the strength of the magnetic field and which brain region or the type of tissue being scanned (e.g., Wansapura, Holland, Dunn, & Ball, 1999; Lin, Bernstein, Huston, & Fain, 2001). Within the context of the current study, it should also be noted that some studies have indicated abnormal T_1 and T_2 relaxation times in schizophrenia patients compared to healthy controls (e.g., Smith, Baumgartner, & Calderon, 1987; Andreasen et al., 1991; Supprian, Hofmann, Warmuth-Metz, Franzek, & Becker, 1997; Pfefferbaum, Sullivan, Hedehus, Moseley, & Lim, 1999). Finally, magnetic fields are rarely perfect, and any spatial inhomogeneities are additive to the T_2 decay, collectively described by the time constant T_2^* .

During an MRI session, RF waves are sent out in continuous pulses. The time between two RF pulses is called *repetition time*, or TR , usually set at around 1-2 seconds (Huettel et al., 2009). Moreover, what is known as the *flip angle* determines how much the net magnetization vector is rotated with respect to B_0 . The raw MR signal is measured after RF excitation has stopped, in a short time period called *echo time*, TE . During this time period the MR signal decays according to the T_2^* constant, and if TE is made sufficiently long (typically 30-50 ms), the MR signal will significantly depend on the local value of T_2^* . It so happens that local T_2^* is slightly longer where there is brain activation, resulting in a slight increase in MR signal.

Signal Detection and Image Formation

It should be noted that in the context of fMRI, the end result is not a photograph of the scanned subject but rather a map of the spatial distribution of some property of nuclear spins (Huettel et al., 2009). If several additional magnetic fields, each varying in strength across space, are superimposed they will cause spins at different spatial locations to precess at different frequencies. The additional fields, called *gradients*, make it possible to separate MR signals coming from different spatial locations, thus generating a map of those different locations (McRobbie, 2007).

The smallest unit of an MR image is a *voxel*, or volume element. Voxels are three-dimensional objects similar to their well known two-dimensional relatives, pixels, or picture elements. The smaller the voxel size, the higher the *spatial resolution* of the image. The downside is that voxel size is proportional to MR signal; too small voxels may not generate enough signal to create high-quality images (Huettel et al., 2009).

When measuring brain function, the process of direct three-dimensional imaging is too slow and the functional MR signal is restricted to one two-dimensional *slice* at a time. Voxels are ordered in rows and columns — a two-dimensional *image matrix* — and all of these slices are added together to create a three-dimensional image. Two terms related to slices are important; the *slice thickness* refers to the width of

the two-dimensional space that will be excited by the RF pulse, and the *slice gap* refers to the space in between those slices. Smaller slice thickness generates higher spatial resolution, but at the cost of smaller contrast-to-noise ratio, which affects the ability to distinguish details. Slice gaps assure that different slice excitations does not interfere with each other. In general, the slice gap is preferred to be as small as possible, since the area in between is not imaged at all (McRobbie, 2007). The *field of view*, or *FOV*, is the square spatial area that constitutes the final image. A small FOV will generate higher resolution and smaller voxel size, but also lower signal strength. Anatomical images are usually collected through *gradient-echo imaging*, a time consuming process with the advantage of generating high-contrast images. For functional purposes, however, time is of essence. A technique called *echo-planar imaging*, or *EPI*, allows for very rapid collection — twenty or more per second — of an entire T_2^* -sensitive image, and has evolved to become the most widely used fast imaging method for fMRI (Huettel et al., 2009).

Image Preprocessing

Prior to statistical analysis the fMRI data usually undergoes a series of preprocessing stages in order to remove artifacts, standardize locations of brain regions to achieve valid and sensitive group analyses, and to increase the signal-to-noise ratio (Lindquist, 2008).

Since functional MR images in general are of low resolution and provide little anatomical detail, results from functional sessions are usually overlaid on a high resolution anatomical image, in a process called *coregistration*. To make group comparisons possible, each individual brain anatomy must be registered to a standardized stereotaxic space. This process is called *normalization* and is usually achieved using a template brain, such as the Talairach coordinate system (Talairach & Tournoux, 1988) or the Montreal Neurological Institute (MNI) brain (Evans et al., 1993). Finally, a preprocessing stage known as *spatial smoothing* is commonly applied to the fMRI data. Spatial smoothing is an imaging technique that utilizes a mathematical operation known as convolution and a numerical matrix known as a kernel. The technique works placing the kernel over an image matrix, averaging data points (i.e., individual voxel intensities) with their neighbours (i.e., neighbouring voxel intensities) and returning a new value for each data point, thus smoothing or blurring the image. The kernel defines the shape of the function used to average neighbouring data points. Most commonly a Gaussian (i.e., normally distributed) kernel is used. The width of a Gaussian kernel is defined as *Full Width at Half Maximum*, or *FWHM*, which simply is the width of the Gaussian at half its maximum value. As the value of FWHM increases the kernel becomes wider thus resulting in more smoothing (Lazar, 2008).

The Hemodynamic Response Function and BOLD Imaging

The groundbreaking *blood-oxygen-level dependent*, or *BOLD* technique was first described in animal studies by Ogawa and Lee (1990), inspired Nobel laureate Linus

Pauling's work detailing the different properties of diamagnetic oxyhemoglobin and paramagnetic deoxyhemoglobin (Pauling & Coryell, 1936). While BOLD is the most popular of fMRI techniques (McIntyre, Richter, Morden, Wennerberg, & Frankenstein, 2003), it is also a very complicated state of affairs that is not yet fully understood (Logothetis & Wandell, 2004; Nair, 2005). The technique relies on interactions between cerebral blood flow, energy demand, and neural activity; interactions that have been described as overwhelmingly complex (Logothetis, 2003).

The brain's energy demands at rest are almost exclusively (99.5%) met by glucose oxidation, which is further processed into adenosine triphosphate, ATP. While constituting a mere 1-2% of the human body mass, the brain consumes 10% of the body's glucose and oxygen supplies and receives 10% of its blood supply (Gjedde, Bauer, & Wong, 2011). Oxidation is an aerobic chemical reaction, meaning it requires oxygen. Respiration binds oxygen to hemoglobin — the primary oxygen transporter in red blood cells — thus creating oxygen saturated oxyhemoglobin. The oxygen is subsequently released at the site of action and the deoxygenated hemoglobin is transported back to the lungs. During functional brain activation, such as when performing a task, local cerebral metabolic glucose rates and cerebral blood flow increase about 50%, causing a local reduction of deoxyhemoglobin; this is called the hemodynamic response, described by the *hemodynamic response function*, or *HRF* (Logothetis & Wandell, 2004). Note that oxy- and deoxyhemoglobin have different magnetic properties. Further discoveries (Ogawa, Lee, Nayak, & Glynn, 1990; Ogawa, Lee, Kay, & Tank, 1990) revealed that these different properties affect the MR signal. The hemodynamic response decreases the local amount of paramagnetic deoxyhemoglobin, which results in increased local T_2^* and thus increased local signal strength. What BOLD fMRI does, put simply, is to measure these local signal differences.

While not a direct measurement of neural activity, several studies have presented experimental data suggesting a linear relationship between neural activity and the hemodynamic response. For instance, BOLD signals have been found to be directly proportional to the average neuronal firing rate (Rees, Friston, & Koch, 2000), as well as directly reflecting the local increase in neural activity as measured by extracellular field potentials (Logothetis, Guggenberger, Peled, & Pauls, 1999; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001).

fMRI Data Acquisition

Functional and anatomical magnetic resonance images were obtained using a 3T GE Signa HDx scanner (General Electric Medical Systems, Milwaukee, WI, USA) with an eight channel head coil. Head cushions were placed around the subjects' head to minimize head movements. An anatomical image was acquired first, using T_1 -weighted Fast Spoiled Gradient Echo (FSPGR) Bravo (TR = 10.9 s; TE = 4.6 ms; flip angle = 13° ; 236 axial slices 3D acquisition; slice thickness 1.2 mm; field of view = 240 mm \times 240 mm in-plane resolution, matrix size = 352 \times 224). Functional images

were acquired with a BOLD contrast sensitive T_2^* -weighted echo planar imaging sequence (TR = 2 s; TE = 25 ms; flip angle = 78°). Each volume consisted of 36 slices acquired approximately parallel to the AC-PC (anterior and posterior commissure) plane (sequential acquisition; slice thickness = 3.5 mm; slice gap = 0.5 mm; 4 mm \times 4 mm in-plane resolution; 64 \times 64 matrix).

SPM8 Preprocessing and Analysis

Preprocessing and analysis of fMRI data was done using Statistical Parametric Mapping, version 8 (SPM8; Wellcome Trust Centre for Neuroimaging, University College London, United Kingdom) implemented in MATLAB, version 8.2 (The MathWorks, Inc., Natick, Massachusetts, United States).

Functional sessions were reviewed for artifacts and extreme variance using the SPM8 toolbox TSDiffAna (Brett & Glauche; <http://www.fil.ion.ucl.ac.uk/spm/ext/-#TSDiffAna>). Functional images were realigned to the first image in the series. The anatomical image was coregistered to the mean image and, using segmentation, spatially normalised to the Montreal Neurological Institute T_1 template (Evans et al., 1993). No subject moved more than 3 mm in any direction. The functional images were spatially normalised using parameters estimated from the segmentation procedure and were resampled to 3 mm isotropic voxels and smoothed using an 8 mm Full Width Half Maximum Gaussian kernel. Data were high-pass filtered using a cutoff value of 128 s. The data were analyzed by modeling ten regressors; six for movement correction and four event types as stick functions convolved with a synthetic HRF. The four events consisted of the CS+ unpaired, CS+ paired, CS- unpaired and CS- paired. The two regressors consisting of CS+ paired and CS- paired were not used in any contrasts. The contrasts CS+ unpaired vs CS- unpaired was specified and moved up to second-level random effects models. Spheric region of interest analysis of the ventral striatum was based on previous coordinates from Jensen et al., (2008).

Cytoarchitectonic areas were identified based on stereotaxic coordinates using the SPM8 toolbox Anatomy, version 1.8 (Eickhoff; http://www.fz-juelich.de/inm/inm-1/DE/Forschung/_docs/SPMANatomyToolbox/SPMANatomyToolbox_node.html).

Functional MR images for results presentation were extracted using the SPM8 toolbox xjView, version 8 (Cui, Li, & Song; <http://www.alivelearn.net/xjview8>).

Self Reports and Statistical Analysis

In a post-scan questionnaire, subjects were asked to rate their degree of uneasiness when the conditioned (CS+) and neutral (CS-) stimuli were shown, on a scale ranging from 1 to 6. Descriptive and clinical data were controlled for normality using the Shapiro-Wilk test. Wilcoxon signed-rank tests were used to investigate differences in rated uneasiness. Mann-Whitney's U, a two sample t-test and χ^2 were used to assess group differences in descriptive data. Pearson's r and Spearman's ρ were used to investigate correlations between symptoms (PANSS ratings) and neural response

(fMRI β values in the ventral striatum) to CS+ and CS-. Statistical procedures were carried out using SPSS Statistics, version 22 (IBM Corporation, Armonk, New York, United States).

RESULTS

Patients showed no evidence of aberrant salience attribution by self report. Both patients (3.18 vs 1.27; $Z = 2.69$, $p = .007$) and controls (3.80 vs 1.40; $Z = 3.09$, $p = .002$) showed significant differences in rated uneasiness for CS+ vs CS- (Figure 2, left panel). Using the fMRI BOLD data differences in neural response were examined. No significant differences within patient nor control groups for the [CS+ > CS-] contrast were obtained in any region of the brain after correcting for multiple comparisons. A two sample t-test investigated differences in brain activation in the ventral striatum using a small volume region of interest (5 mm radius sphere, peak at coordinates 6, 5, 1) for the contrast [CS+ > CS-]. After controlling for family-wise errors, patients showed a significantly stronger activation compared to controls, $t(25) = 2.96$, $p_{FWE} = .022$, $Z_{equiv} = 2.71$, extent of voxels = 16 (Figure 3). An investigation of β values revealed that the significant difference for the [CS+ > CS-] contrast was due to patients' stronger neural response to the CS+ compared to the CS-, while controls displayed an opposite pattern (Figure 2, right panel).

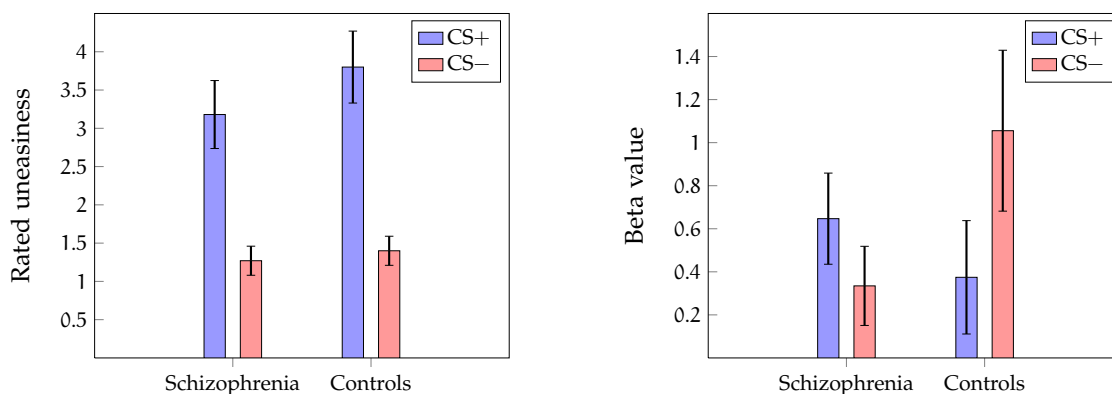


Figure 2. The left panel shows subjective ratings of uneasiness for the two conditions. The right panel shows β values for the two conditions in the ventral striatum (at coordinates 6, 5, 1). The error bars represent SE.

An uncorrected whole brain analysis revealed two clusters (voxel size ≥ 3) of significant difference in activation for the [CS+ > CS-] contrast. The first cluster showed a greater difference in activation in the right inferior frontal gyrus for patients, $t(25) = 3.93$, $p_{uncorr} < .001$, $Z_{equiv} = 3.42$, extent of voxels = 6, peak at coordinates 30, 11, 34 (Figure 4, left panel), and the second cluster showed a greater difference in activation in the right angular gyrus for patients, $t(25) = 3.53$, $p_{uncorr} = .001$, $Z_{equiv} = 3.13$, extent of voxels = 3, peak at coordinates 57, -58, 25 (Figure 4, right panel).

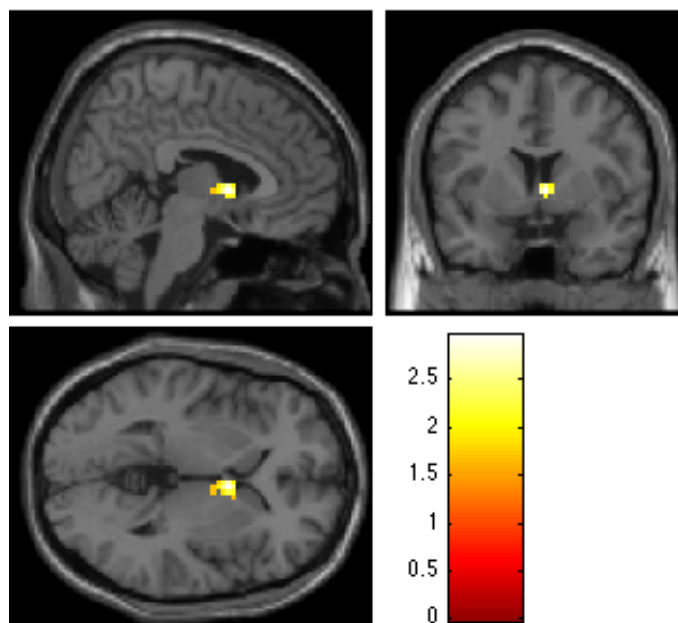


Figure 3. A statistical parametric map showing the significantly stronger activation in the ventral striatum for the contrast [CS+ > CS-] in schizophrenia patients (N = 11) compared to healthy controls (N = 15). Colors refer to t-values.

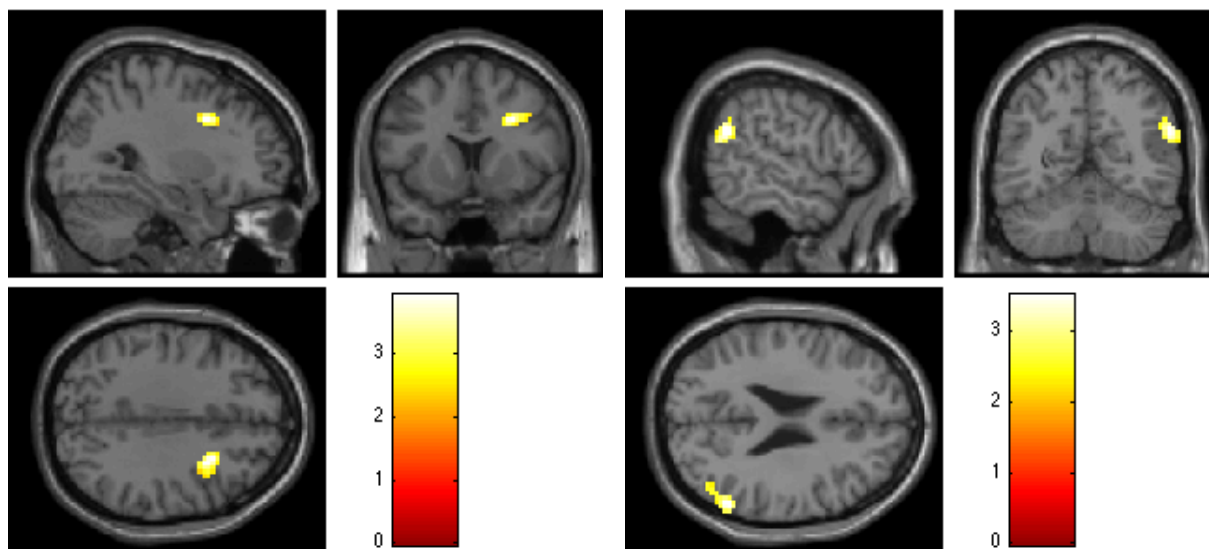


Figure 4. Statistical parametric maps showing the significantly stronger activation in the right inferior frontal gyrus (left panel) and the right angular gyrus (right panel) for the contrast [CS+ > CS-] in schizophrenia patients (N = 11) compared to healthy controls (N = 15). Colors refer to t-values.

No significant correlations between symptoms (PANSS positive, $n = 11$, $\rho = .06$, $p = .863$; PANSS negative, $n = 11$, $\rho = -.10$, $p = .765$; PANSS total, $n = 11$, $\rho = -.29$, $p = .383$; PANSS general, $n = 11$, $\rho = -.29$, $p = .384$) and neural response to CS+ was found among the patients. Neither were any significant correlations between symptoms (PANSS positive, $n = 11$, $r = -.50$, $p = .114$; PANSS negative, $n = 11$, $\rho = -.54$, $p = .088$; PANSS total, $n = 11$, $\rho = -.37$, $p = .269$; PANSS general, $n = 11$, $r = -.37$, $p = .269$) and neural response to CS- found among the patients.

DISCUSSION

Patients showed no evidence of aberrant salience attribution neither by self-report nor in neural response. No significant within group differences in neural activation in response to the [CS+ > CS-] contrast were found in any region of the brain after correcting for multiple comparisons. No significant correlations between PANSS ratings and β values for CS+ nor CS- were found. Significant differences in neural activation between patients and controls were found in the ventral striatum, right inferior frontal gyrus, and the right angular gyrus for the [CS+ > CS-] contrast.

Significant Differences in Neural Activation

Patients showed a greater difference in brain activation in the ventral striatum for the [CS+ > CS-] contrast compared to healthy controls. Upon investigation the result was revealed to be due to healthy controls showing stronger neural response to the CS- condition than did the patients, while patients showed stronger neural response to the CS+ condition than did controls. The result is a direct opposite of what previous studies (e.g., Jensen et al., 2008; Diaconescu et al., 2011) have shown, and is as surprising as it is difficult to explain. The result is confounding, since it indicates a greater degree of aberrant salience attribution in the healthy control group than in the schizophrenic group, and to the authors knowledge there exists no previous theoretical justification. A tentative explanation would be a combination of the region of interest analysis (where only a small volume was examined), low statistical power, and patients' low PANSS ratings. Speculatively, being in an extreme laboratory environment with noises and an unfamiliar experimental task might also have contributed to healthy subjects abnormal neural response. However, why this would affect healthy subjects more than patients remains unclear.

Evidence suggesting that psychosis manifests on a continuum rather than at clearly defined borders (e.g., clinical vs non-clinical) provide an alternative explanation (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). For instance, Balog, Somlai and Kéri (2013) replicated Jensen's et al. (2008) study using healthy volunteers assessed with the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; Mason, Claridge, & Jackson, 1995). The study showed that psychosis related O-LIFE scores (reality distortion and withdrawal traits) significantly predicted lower responses to conditioned stimuli (i.e., CS+), and that reality distortion also was associated with an enhanced representation of neutral events (i.e., CS-). While it appears that no direct comparisons between O-LIFE and PANSS exist, Balog, Somlai and Kéri (2013) showed that even in healthy subjects some degree of aberrant salience is present, persistent with the idea of a psychosis continuum. While unlikely in the face of previous studies, it does seem possible that the healthy controls in the current study could have exhibited greater levels of aberrant salience than patients.

A larger difference in neural activation in the right inferior frontal gyrus (IFG) was found for the [CS+ > CS-] contrast in schizophrenia patients compared to healthy

controls. The cytoarchitecture of the IFG is diverse and related both to speech, language and auditory processing (e.g., Greenlee et al., 2007). An fMRI study using a passive listening task found that expectancy alone of an auditory stimuli modulated IFG activity in healthy subjects (Osnes, Hugdahl, Hjelmervik, & Specht, 2012). The right IFG has previously been linked to auditory hallucinations in schizophrenia patients, and while the functional anatomy has yet to be fully established, theories point in the direction of auditory hallucinations being abnormal activation of regular auditory neural pathways (Lennox, Park, Medley, Morris, & Jones, 2000). Studies have found functional and anatomical connectivity abnormalities in the both the left and right IFG in schizophrenia patients (e.g., Jeong, Wible, Hashimoto, & Kubicki, 2009), though it has been suggested that the majority of schizophrenia patients show activations in the right IFG and functionally related areas during auditory hallucinations (Sommer et al., 2007; Sommer et al., 2008; Diederer et al., 2010). Despite patient's relatively low ratings ($M = 2.18$, $SD = .98$) for the PANSS hallucinations variable (P_3) in the current study, it possible that a combination of stimulus expectancy and auditory hallucinations produced the observed difference in activation for patients vis-à-vis controls.

Schizophrenia patients also displayed a larger difference in neural activation in the right angular gyrus (AG) for the [CS+ > CS-] contrast compared to healthy controls. The angular gyrus is part of the inferior parietal lobule (IPL), an area dealing with attention, memory and language processing; processes that appear to be abnormal in schizophrenia (Niznikiewicz et al., 2000). The AG is also thought to serve an important role in the conscious experiences of one's own actions, such as the sense of agency and the awareness that an intended action is consistent with subsequent movement (Farrer et al., 2008), as well as attentional processing of visual feedback (Desimone & Duncan, 1995). Despite its apparent importance, relatively few studies have investigated the AG in relation to schizophrenia (see Torrey, 2007, for a review). A recent study using a semantic priming paradigm showed that schizophrenia patients display increased neural response in the right AG compared to healthy controls (Sass et al., 2014), which may reflect semantic processing abnormalities in schizophrenia. Given the rather unknown functional relevance of the AG in relation to schizophrenia, it is difficult to pinpoint why patients differed in neural response compared to controls in the current study. It may be related to their sense of agency or awareness of actions while being placed in an MR scanner or their processing of visual feedback during the experimental session. It may also reflect some kind of semantic processing abnormality, perhaps related to auditory hallucinations and the right inferior frontal gyrus, as discussed above.

Lack of Evidence for Aberrant Salience Attribution

The study found no evidence for aberrant salience attribution, and while there may be a multitude of reasons underlying this result, two explanations emerge as particu-

larly plausible; to the low number of subjects in the two conditions, and the relatively low symptom ratings for patients.

As should be well known, statistical power is defined as the probability of rejecting the null hypothesis when it is false. Three major factors influence power: (1) the size of the effect, which is the difference of means and variance between the experimental and control conditions, (2) the chosen α value and (3) the sample size (Desmond & Glover, 2002). Of these three sample size is, at least in theory, the easiest for the experimenter to manipulate, yet subject to practical constraints such as costs and limited access to scanners and, foremost, patients.

Unfortunately, power analyses for fMRI studies have been sparse and little is known about how many scans, trials or subjects are necessary for reliable results. A first estimate of the number of required subjects suggested a minimum of 12 in order to achieve 80% power at the single voxel level, using an α threshold of 0.05 and spatial smoothing of 5 mm FWHM. More realistic thresholds such as correcting for multiple comparisons required doubling the number of subjects to maintain power at 80% (Desmond & Glover, 2002). A follow-up study yielded similar results, suggesting that fMRI studies using typical subject numbers ($N = 10-20$) are underpowered (Murphy & Garavan, 2004). The authors note that studies using $N = 15$ subjects may not necessarily be inaccurate, but rather incomplete; activation areas are most likely true positives, yet with a sizeable number of false negatives. While it must be acknowledged that both studies based their estimates on block designs, which may not carry over to event related designs, it appears that the sample used ($N = 11$ for patients and $N = 15$ for controls) in the current study was decidedly underpowered. In reference to the above discussion of psychosis as a continuum, it should be noted that the Balog et al. (2013) study employed skin conductance responses and reaction time, not fMRI, affording the authors a much greater sample size ($N = 100$) and thus, greater power to detect any effect.

Furthermore, previous research has shown that the spatial extent of BOLD signal activation increases as the number of single trials averaged increases. If the goal is to detect the presence of active voxels within a certain region of interest, a relatively small number (< 20) of trials may suffice. On the other hand, if the goal is to determine the spatial extent of activation for more or less all active voxels, far more (> 100) trials are necessary (Huettel & McCarthy, 2001). The 80 trials per subject used in the current study may well suffice for region of interest analyses, yet may be too low for detecting the spatial extent of activations in whole brain analyses, and thus may partly explain the lack of significant differences when multiple comparisons were corrected for.

A second possible explanation for the results emanates from the rather low symptom ratings obtained across the patient sample. Previous studies using unmedicated schizophrenia patients have reported PANSS ratings at noticeably higher levels than what was observed in the current study (Table 2).

A closer inspection of the delusions variable (P_1) in the PANSS positive subscale revealed a mean value of 2.27 ($SD = 1.49$) for patients in the current study. Patients

Table 2. Symptom ratings ($M \pm SD$) in studies with unmedicated schizophrenia patients.

Study	PANSS Total	PANSS Positive	PANSS Negative	PANSS General
Juckel et al. (2006)	92.8 \pm 23.7	26.3 \pm 7.6	23.1 \pm 7.0	NA
Esslinger et al. (2012)	91.0 \pm 20.4	21.5 \pm 6.9	21.9 \pm 7.4	47.6 \pm 11.0
Nielsen et al. (2012)	86.0 \pm 15.0	21.0 \pm 4.4	22.0 \pm 6.9	43.0 \pm 8.0
Schlagenhauf et al. (2014)	85.6 \pm 16.2	22.2 \pm 5.8	21.6 \pm 5.9	41.8 \pm 10.0
Current study	47.55 \pm 12.52	12.09 \pm 4.55	9.55 \pm 3.21	25.00 \pm 7.23

thus were, on average, categorized either slightly above a rating of 2, denoting minimal, questionable or subtle pathology, or moderately below a rating of 3, denoting mild, clearly established but not pronounced pathology (Opler, Opler, & Malaspina, 2006). Consequently, a reasonable explanation for the lack of aberrant salience attribution in the current study would be that the psychotic symptoms were not severe enough to be detected at the time of the experiment. This might be related to the fact that the patients included in the current study were diagnosed along the schizophrenia *spectrum* as opposed to schizophrenia alone, which also ties in with the above discussion of healthy volunteers also exhibiting some degree of aberrant salience.

Patient's low symptoms ratings combined with low statistical power would also serve as an explanation for the lack of significant correlation with neural response to the CS+ and CS- conditions, in line with previous findings from Jensen et al. (2008). While insignificant, the correlations between CS- and PANSS positive ($r = -.50, p = .11$) as well as PANSS negative ($\rho = -.54, p = .088$) were strong (Cohen, 1988), indicating lack of statistical power.

Ethical Considerations

While the study was approved by the Regional Ethics Committee, a few ethical considerations deserve to be acknowledged. The American Psychological Association (2010) provide guidelines for conducting ethical research, stating that psychologists should "make reasonable efforts to avoid offering excessive or inappropriate financial or other inducements for research participation when such inducements are likely to coerce participation" (p. 11). The patients in the current study received payment for their participation, and were also recruited from non-institutional care in part because they had been medication free for at least two months. In such cases there is a risk that patients decline medicine due to the financial gain of being part of the study. All participants received financial compensation at a level judged not to impose any obligation to participate, and patients were at all times guaranteed medication if deemed necessary.

Summary and Suggestions for Future Research

Despite the lack of convincing evidence for the aberrant salience hypothesis, the current study is not without merit. It would be a fair assumption that a large portion of schizophrenia research is based upon the dopamine hypothesis, yet most studies recruit schizophrenia patients treated with dopamine antagonists. It is a very time-consuming effort to recruit schizophrenic patients that are not subject to antipsychotic medications and while the number of subjects included may have rendered the study underpowered, the study of unmedicated schizophrenia patients in an aversive Pavlovian conditioning paradigm constitutes a unique contribution to the field. Furthermore, given the extreme laboratory environment involved, recruiting subjects and performing experimental tasks with unmedicated patients displaying more severe PANSS ratings would be both difficult and ethically more demanding.

Nevertheless, the current study should be replicated using a larger subject sample in order to investigate if the conflicting results remain. The use of aversive conditioning — owing to its realistic relation to psychosis (Balog, Somlai, & Kéri, 2013) — should be emphasized. Future studies should also pay attention to the right inferior frontal gyrus as well as the right angular gyrus, and further investigate their relationship to aberrant salience during aversive conditioning, and to schizophrenia at large.

As the psychopathology of schizophrenia unfolds, psychosis and its delusional content does not seem to be inescapably determined by biology, but rather described as a dynamic phenomenon linked to both neurobiology and cognitive processes (e.g., Kapur, 2003). While aberrant salience attribution in itself might be chemically driven by chaotic dopamine transmission, the higher-level, non-sensory cognitive explanations that shape delusional content in order to bring consistency and relief are culturally and psychodynamically determined (Kapur, 2003; Schmack et al., 2013). Current research would suggest that not only pharmacotherapy but also psychotherapy should be implemented in the treatment of schizophrenia.

If the delusional content during psychosis is related to aberrant salience and context-inappropriate associations — as previous studies suggest, even though the current study failed to corroborate — clinicians should address such issues and help patients recognize what is real and what is not, and aid patients in learning how to differentiate between normal and abnormal salience and associations. Herein lies perhaps the greatest challenge, but studies using meta-analysis have shown that cognitive behavioural therapy may be an effective treatment of schizophrenia patients with both positive and negative symptoms (Gould, Mueser, Bolton, Mays, & Goff, 2001; Wykes, Steel, Everitt, & Tarriner, 2008; Jauhar et al., 2014), and group therapy has shown to be effective in first-episode or recent onset psychosis (Chung, Yoon, Park, Yang, & Oh, 2013).

Future research should also investigate potential neurobiological changes, both in the ventral striatum and other areas, in response to cognitive therapy. This has been done using medicated schizophrenia patients (Kumari, Antonova, Fannon, & Peters, 2010; Kumari et al., 2011), yet to the authors' knowledge not with unmedicated pa-

tients, which would be a natural next step. On a neurochemical level, although the dopamine hypothesis has a proven heuristic value, it might also be time to focus more on a multifactorial view, involving interactions between monoamines, glutamate, and γ -aminobutyric acid (Carlsson et al., 2001). Further insights into the chemical basis of schizophrenia should hopefully help advance the field of antipsychotic medicine, which when used in conjunction with proper therapy ought to improve the lives of those suffering under schizophrenia spectrum disorders.

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