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Review

Genuine and drug-induced synesthesia: A comparison

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ABSTRACT

Despite some principal similarities, there is no systematic comparison between the different types of synesthesia (genuine, acquired and drug-induced). This comprehensive review compares the three principal types of synesthesia and focuses on their phenomenological features and their relation to different etiological models. Implications of this comparison for the validity of the different etiological models are discussed.

Comparison of the three forms of synesthesia show many more differences than similarities. This is in contrast to their representation in the literature, where they are discussed in many respects as being virtually similar. Noteworthy is the much broader spectrum and intensity with the typical drug-induced synesthesias compared to genuine and acquired synesthesias. A major implication of the phenomenological comparison in regard to the etiological models is that genuine and acquired synesthesias point to morphological substrates, while drug-induced synesthesia appears to be based on functional changes of brain activity.

Contents

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1. Introduction

Synesthesia (Greek: syn = together; aesthesis = perception) is usually defined as a crossing of sensory perceptions, where stimulation within one sensory modality/stream leads to an internally generated perceptual experience of another sensory modality/stream. The stimulated percept is called the inducer whereas the additional perceived percept is called the concurrent (Grossenbacher & Lovelace, 2001), and the type of synesthesia is named the inducer-concurrent pair (e.g. auditory–visual synesthesia where acoustic stimulation leads to a visual experience). Synesthesia is not restricted to inter-modal couplings but can also occur within a modality. An example is grapheme-color synesthesia where coupling between written letters and color is experienced.

According to Grossenbacher and Lovelace (2001), we can differentiate three forms of synesthesia:

1. Constitutional or genuine synesthesia.
2. Acquired synesthesia.
3. Drug-induced synesthesia.

In genuine synesthesia, the inducer-concurrent coupling is experienced the entire life.

Acquired synesthesia can be experienced after brain damage (Jacobs, Karpik, & Bozian, 1981; Ro et al., 2007) or sensory deafferentation (Armel & Ramachandran, 1999). In this type the concurrents are usually referred to as phosphenes. A phosphene (an inadequate stimulus to the photoreceptors (Kandel, Schwartz, & Jessell, 2000)), is a visual phenomenon elicited by stimulating the retina mechanically, electrically (Penfield & Rasmussen, 1957), magnetically (Eichmeier & Höfer, 1974), or by direct stimulation of the occipital cortex (Cowey & Walsh, 2000).

Drug induced synesthesia is experienced temporarily during acute effects of a hallucinogen (mescaline, psilocybin, LSD) drug intoxication (Beringer, 1927; Friedrichs, 2009; Shanon, 2002). During intoxication, a dream-like state of consciousness is typical, accompanied by changes in the relationship between the sense of self and the cosmic, an intensification of affectivity (Masters & Houston, 1966), a decrease of self-control, and a change in time perception and thinking abilities (Vollenweider, 2001; Wittmann et al., 2007). Additionally, an intense inner flow of sensations is often experienced accompanied with hallucinatory activity, especially in the visual sphere (Hoffer & Osmond, 1967; Studerus, Gamma, & Vollenweider, 2010). In reviewing all the manifold effects of hallucinogenic drugs, it becomes clear that synesthesia is only one possible aspect of the intoxication. A major effect of hallucinogenic drugs is the intensification of sensory perception, including illusions, pseudo-hallucinations, and, in very rare cases, true hallucinations (Leuner, 1962).

During the acute effects (cf. Table 1), the first phase of the intoxication usually induces hallucinatory phenomena that are more simple in design like abstract geometric forms (“entoptic phenomena” or “Form constants” (Klüver, 1966)). As the course of intoxication progresses (or with higher dosage), the visual phenomena change to more complex forms and may even develop into coherent scenes seen on a kind of “inner screen” (Friedrichs, 2009).

Much has been written about genuine synesthesia (Bleuler & Lehmann, 1881; Cytowic, 2002; Harrison & Baron-Cohen, 1995; Hochel & Milan, 2008; Hubbard, 2007; Marks, 1975; Mattingley, 2009; Ward & Mattingley, 2006), but the other forms have been somewhat neglected. Drug induced synesthesia is reported, but, until now, there were no systematic studies (see (Shanon, 2002)). The same is true for acquired forms. Most papers available are neurological descriptions of single cases where the type of damage and effect is reported (Armel & Ramachandran, 1999; Jacobs et al., 1981; Kim, Dryja, Lessell, & Gragoudas, 2006; Koike & Yoshino, 1990; Lessell & Cohen, 1979; Page, Bolger, & Sanders, 1982; Rao, Nobre, Alexander, & Cowey, 2007; Ro et al., 2007; Steven & Blakemore, 2004; Vike, Jabbari, & Maitland, 1984), but systematic investigations are missing.

All these phenomena are discussed separately and are not compared directly. Yet such comparisons are of importance in order to shed light on the mechanisms underlying synesthetic perception. Is the phenomenology of the different types comparable? Are there commonalities in the current etiological models? Can knowledge about one form be transferred to the others? Or are these types too different to even speak of a “unitary” phenomenon?

Table 1
Visual and synesthetic phenomena during the course of acute hallucinogen effects (psilocybin 20 mg p.o.) (Grof, 1975; Heimann, 1961; Leuner, 1962).

	30–75 Min	>75-Min	240–350 Min.
Visual phenomena	Abstract geometric patterns Klüver's form constants entoptic phenomena	Complex organic imagery Scenic imagery	Decrease and fading of imagery
Synesthetic phenomena	More automaticity	Less automaticity	

This paper evaluates the similarities and differences between different types of synesthesia, their phenomenology, and relevant etiological models. In the first part we directly compare important phenomenological features. Afterwards, an overview of the current etiological models is presented. The discussion provides a critical synopsis of the comparative data as well as an outlook about recent and future research needs.

2. Phenomenological comparison

Different aspects of the synesthetic phenomenon can, in comparison of sub-types, lead to a better overall understanding of synesthesia. In this part the different forms of synesthesia are compared on a set of dimensions:

2.1. Consistency

Consistency is one of the hallmarks of *genuine synesthesia* which can be described by a high inter- and low intrapersonal variance between inducer-concurrent couplings (Baron-Cohen, Wyke, & Binnie, 1987; Eagleman, Kagan, Nelson, Sagaram, & Sarma, 2007). A high consistency or low intrapersonal variance means that the same inducer always induces the same concurrent. The couplings are stable over decades (Simner & Logie, 2007) and virtually all older synesthetes report that there have been no changes during their lifetime (i.e. the letter 'A' is always red for a certain synesthete). Thus, genuine synesthesia is experienced the whole life. Due to its idiosyncrasy (Cytowic, 2002), inter-individual variance is quite high.

Mapping to the concurrent develop and stabilize when synesthetes learn written letters in school (Simner, Harrold, Creed, Monro, & Foulkes, 2009). Consistency is used in order to diagnose genuine synesthesia in the 'test of genuineness' (Baron-Cohen et al., 1987; Eagleman et al., 2007). But some researchers question the criterion of consistency for the diagnosis of genuine synesthesia and try to define synesthesia neurologically as the result of 'hyper-association' between brain regions (Simner, 2012). Here it is argued that the consistent mapping found in most described synesthetes may be due to a selection bias and that there might be types of genuine synesthesia which are not consistent at all.

Acquired synesthesia is not consistent, but no systematic investigations have to-date been completed. In a single case study, the subject developed stable sound-touch pairings (Ro et al., 2007) suggesting that, once developed, the synesthetic coupling is stable. But if looking closely at the available reports, the coupling is not really consistent, as the same inducer might evoke different concurrents on different occasions (Jacobs et al., 1981). This discrepancy is due to the fact that often many inducers can elicit only a single concurrent (a simple flash) and this looks like a stable mapping as every time the same concurrent is triggered. But if more concurrents are involved the mapping is unstable. Due to the rather small spectrum of possible inducers and concurrent, intra- and interpersonal variance is rather low.

Drug-induced synesthesia is a much more flexible phenomenon (Beringer, 1927). The same tone might be red, but, when repeated, it may be experienced as another color (or even translated into another sensory modality). Thus, there are no consistent inducer-concurrent couplings (Beringer, 1927; Friedrichs, 2009), but there are highly idiosyncratic mappings leading to a high inter- and intrapersonal variance. Nevertheless, highly associative stimuli may induce more consistent mappings during specific conditions, characterized by low intra- and interpersonal variance.

2.2. Automaticity

Genuine synesthesia is an automatic process. As soon as synesthetes recognize an inducer, their concurrent is triggered. Indicative for the automaticity is the synesthetic Stroop effect that makes it more difficult to name the true color of a colored inducer when it is presented in a color different from the synesthetic color (Mills, Boteler, & Oliver, 1999).

As an automatic process the synesthetic experience is not controllable by the synesthete and the synesthetic percept cannot be willed to change. A marginal controllability is exerted via the attention system, as attention is required in order to elicit synesthesia (Mattingley, Rich, Yelland, & Bradshaw, 2001). If the synesthete ignores the inducer then the concurrent is not perceived. An example is reading. Some synesthetes report that letters (but not words) are colored. When such a synesthete reads, no colors are perceived as he reads words and not letters (even though words consist of letters). But even if words are colored, most synesthetes are able to ignore the colors when reading through, concentrating on the content. Thus, triggering of synesthesia can be controlled through ignoring the inducer.

In *acquired synesthesia*, automaticity has not yet been explored in detail. In a single case study (Ro et al., 2007), the subject only responded to the stimuli in a synesthetic manner around 80% of the time. That would mean that automaticity is not given in the acquired form, as one out of five inducers would not induce a synesthetic perception. Also other descriptions point to this direction, as the amount of perceived synesthetic experiences varies greatly between subjects, form up to 10 times per night to three times per year (Jacobs et al., 1981).

The synesthetic concurrent cannot be changed willingly; at least it is not reported. Here an indirect influence can be obtained by controlling the overall state the subject is in, as some states like drowsiness are more likely to elicit synesthesia (Page et al., 1982).

In *drug-induced synesthesia*, the synesthetic experience is not automatic. It can be experienced during intoxication but may also be absent (Studerus, Kometer, Hasler, & Vollenweider, 2010). Also when synesthesia is experienced during the intoxication, a stimulus may (but not always) elicit synesthesia. And even if a stimulus is perceived synesthetically on

occasion, this effect may vanish when approached a second time. A higher dose increases the chance for experiencing these effects (Delay, Gérad, & Racamier, 1951; Leuner, 1962; Masters & Houston, 1966).

The controllability is also dose-dependent as well as dependent on the individual and his/her experience to handle the drug-induced state. For example, drug-induced synesthesias can be alleviated by opening the eyes or focusing on abstract thinking or other cognitive processes as well as paying more attention to the environment (especially change of locale from inside to outside or vice versa). The specific inducer-concurrent pairing, which appears spontaneously during the drug's effects is usually virtually impossible to be influenced or altered by conscious control (Masters & Houston, 1966; Shanon, 2002).

2.3. Phenomenology of inducers

In *genuine synesthesia*, the inducer typically falls in the class of ordinal over-learned sequences like numbers, the alphabet, months of the year, and days of the week (Day, 2004; Novich, Cheng, & Eagleman, 2011; Shanon, 1982). But also sounds, music, voices, moving patterns, smell, taste, or tactile stimulation can trigger synesthetic concurrents. Thus, all senses can act as inducers. In the case of ordinal sequences, synesthesia is triggered independent of the presented modality. Visual (Mills et al., 1999) or acoustical presentation (Baron-Cohen et al., 1987) of the inducer and even merely thinking about it will elicit synesthesia (Dixon, Smilek, Cudahy, & Merikle, 2000). Interestingly, sensory perceptions of things external to the body are the only capable inducers as there are no reports of proprioceptive or vestibular stimuli as inducers. An exception is acute pain, but here also the distinction of exteroceptors/interoceptors becomes somewhat unclear. Genuine synesthesia is the only form where cognition plays a great role in inducing it (Mroczko, Metzinger, Singer, & Nikolic, 2009). For example, in grapheme-color synesthesia not the form of a letter but its interpretation, classification, and context trigger the exact color (Bargary, Barnett, Mitchell, & Newell, 2009; Dixon, Smilek, Duffy, Zanna, & Merikle, 2006; Myles, Dixon, Smilek, & Merikle, 2003).

Also, common forms, like weekdays-color synesthesia (the most common form of genuine synesthesia (Simner et al., 2006)), reveal the significance of cognition as, for example, weekdays are a concept which cannot be sensed or encountered in everyday life. This shows that there is a strong impact of the cognitive conceptualization of the inducer in genuine synesthesia.

In *acquired synesthesia*, all sorts of sounds, but not music, can act as inducers (Afra, Funke, & Matuso, 2009), yet touch is also reported (Armel & Ramachandran, 1999). Often, unexpected or startling sounds induce visual phosphenes (Page et al., 1982). The inducer is quite simple and no cognitive components seem to be involved. Over-learned ordinal sequences play no role at all.

In *drug-induced synesthesia*, all kinds of sensory stimulation (but not ordinal sequences) can lead to visual experiences (Shanon, 2002). Music or sounds are most often reported as inducers, but also haptic, gustatory, olfactory, pain, or emotional stimuli can be translated, mainly to the visual domain (Leuner, 1962). Synesthetic effects are more likely the result of how a message is assessed emotionally rather than what the content is (Delay et al., 1951; Mayer-Gross, 1931).

2.4. Phenomenology of concurrents

In *genuine synesthesia*, most reports are of colors as the concurrent where the whole visible color spectrum is possible. Even non-real colors can be experienced, so called 'Martian Colors' (Ramachandran & Hubbard, 2001). Some synesthetes claim that they have not seen their synesthetic colors in reality and have great difficulties in defining the exact color. Even when the concurrent colors are within the visible spectrum, synesthetes have problems identifying these colors as they are most often not 100% satisfied with their choice. Each synesthete has his/her unique color set which does not change over time. But also inter-individual trends are reported (Beeli, Esslen, & Jäncke, 2007; Simner et al., 2005). Synesthetes associate higher frequency graphemes with higher frequency color terms, so that colors often used in a language are coupled with often used letters. Sometimes the color is accompanied by a form/structure and texture (Eagleman & Goodale, 2009). When shapes are involved, they have a close resemblance to Klüver's form constants (Cytowic, 2002; Klüver, 1966). They consist of blobs, spirals, lines, points, and other simple geometric forms (if the concurrent has a geometrical dimension). Complex scenes or realistic pictures are usually not described as concurrents.

When music is the inducer, the concurrent forms will move and change with the music. However, taste can be a more complex concurrent. In one case (Ward & Simner, 2003), a lexical–gustatory synesthete perceives tastes like 'bread soaked in tomato soup' or other complex taste experiences. Another exception is ordinal linguistic personification (OLP) where a personality trait or a persons characters act as a concurrent (Simner & Holenstein, 2007).

Then there are a few cases where smell, touch, sound, temperature, or pain is synesthetically perceived. Again, as in the case of the inducers, it appears that sensory perception of external stimuli takes a dominant role, as there are no reports of hunger or near-syncope being concurrents. The concurrent follows an all-or-nothing response. Either it is there or not, but it is not dependent on the strength of the inducer. An exception (which only involved two subjects and has not been reported in others) is described by Hubbard and colleagues, in which the concurrent depends on the contrast of the inducer and the position on the retina (Hubbard, Manohar, & Ramachandran, 2006). When the contrast was too low or the inducer was located in the periphery of the visual field, no concurrent color manifested.

Table 2
Visual phenomena typically reported by users of hallucinogenic drugs (Siegel, 1975; West, 1962).

Type	LSD	Peyote
Simple	11	58
Complex	5	27
Chromatic	11	22
Abstract	11	
Geometric	9	
Non-patterned	2	
Conventional forms and objects	5	
Random		6
Line		5
Curve		8
Web		0
Lattice		13
Tunnel		15
Spiral		4
Kaleidoscope		7
Animal and Humans		12

Table 3
Typical dose ranges of some classical hallucinogens (Brimblecombe & Pinder, 1975; Shulgin, 2003).

Compound and route of administration	Low dose	Medium dose	High dose	Duration of action
LSD (p.o.)	50–100 mcg	100–200 mcg	200–500 mcg	7–10 h
Mescaline (p.o.)	200–300 mg	300–450 mg	450–600 mg	9–12 h
Psilocybin (p.o.)	10–15 mg	15–25 mg	25–35 mg	3–6 h
Dimethyltryptamine (i.m.)	25–50 mg	50–75 mg	75–100 mg	30–45 min

The concurrent does not lead to confusion. Synesthetes are usually able to differentiate real experience from synesthetic experience, so there is no confusion between "normal" and "synesthetic" perceptions. Sometimes they say something like "synesthetic colors are more transparent" or "I have never actually seen colors like those I experience in synesthesia." Thus, even though the concurrent has perceptional dimensions, it is distinct from "real" perception.

In *acquired synesthesia*, most often phosphene-like colored flashes (Page et al., 1982), flashbulbs, kaleidoscopic, flames, or ameba-like or plaid-like structures (Jacobs et al., 1981) partially identical with Klüver's form constants (Klüver, 1966) or the so-called phosphenes (Oster, 1970), but no complex forms, are reported as concurrents. If color is involved most often blue/white and dull yellow are described (Page et al., 1982), but also pink, red, and green are possible (Jacobs et al., 1981).

In *drug-induced synesthesia*, the most common concurrents are visual. The visual/synesthetic imagery can be divided into two categories (Grof, 1975; Siegel, 1975). With low doses or during the initial phase with higher dosages of hallucinogens, experiences of abstract geometric imagery are typically part of the spectrum of effects (cf. Table 2). This type of imagery is often compared to Arabic carpet-like designs and related to the so-called range of typical form-constants as discovered by Klüver in 1928 (Klüver, 1966). The other type of imagery is much more complex and only to be experienced with medium or higher doses (cf. Table 3) (Friedrichs, 2009; Grof, 1975; Leuner, 1962).

In this imagery, complex scenes, usually derived from personal memories or fantasies, are experienced as the concurrent (Leuner, 1962). Such concurrents can go on for a few seconds up to a few minutes. Such "visions" are experienced in colors and only rarely in black and white. Most often the three basic colors red, yellow, and blue are reported (Siegel, 1975; West,

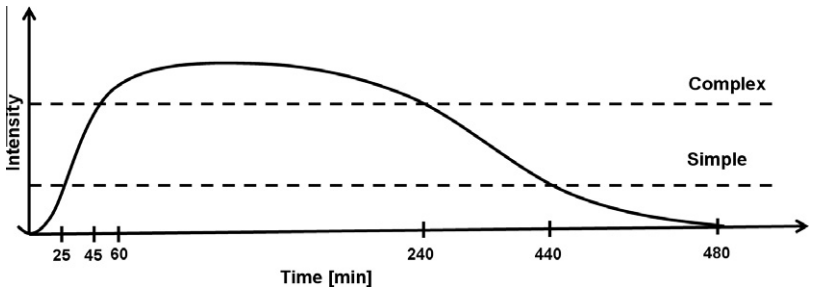

Fig. 1. Typical course of the acute clinical effect of a medium dose LSD (175 μg p.o.) modified from (Leuner, 1962). Shown is the degree of intensity of the drugs effects which are related to the degree of complexity of the visual/synesthetic subjective experience. Simple forms are dominant with lower degrees of intensity, while with higher dosage/intensity the more complex imagery/synesthesias are dominant.

1962), but all colors are possible. Usually these visual phenomena come within a flow of inner experiences, which is usually integrated with the appropriate emotions. Both types of imagery, the primitive and complex forms, can be easily influenced by sensory stimuli, especially those from the acoustical sphere, but also from all other sensory modalities. For example, soft music was employed in most settings with the use of these drugs to stimulate or intensify these kinds of visual dream-like imagery (Abramson, 1967). In both (primitive and complex) forms of visual imagery, synesthetic perceptions are possible, but their dose-dependency makes it clear that the more complex forms are more synesthesia-prone than the primitive ones (Siegel & Jarvik, 1975). For a schematic time course see Fig. 1.

The concurrent constantly changes, and we also find feedback effects. A flow of inner experiences, integrated with the appropriate, but enhanced affectivity, is manifesting within the drug user. This flow may be altered or influenced by incoming acoustical, olfactory, haptic (Friedrichs, 2009; Mayer-Gross, 1931) or synesthetic phenomena, so that the dynamics of the experience are not completely altered in regard to general content or direction but can be partially influenced by the introduced synesthetic phenomena. These may even change the general course of the flow of inner experiences, but usually they are only accompanying it (Strassman, 1995). This implies that the synesthetic phenomena are an integral part of the flow of inner experiences and therefore correlate to the complexity and dynamics of the inner experience with the experiential field (Leuner, 1962; Masters & Houston, 1966).

Stimuli from different modalities may also induce synesthetic global changes in the visual field, for example changes of brightness and/or dominant color (Siegel & Jarvik, 1975). In rare cases, acoustical, visual, haptic or olfactory stimuli may lead to grave alterations of the sense of one's body or body scheme (Mayer-Gross, 1931). Some descriptions of acoustical stimuli inducing experiences of pain have been reported, as well (Friedrichs, 2009).

2.5. Location (outer world/inner screen)

Dixon, Smilek, and Merikle (2004) proposed a classification system between projector and associator synesthetes who have *genuine synesthesia*. Projectors see the inducer within the real world, on the location where the inducer is perceived. Associators, on the other hand, see the concurrent in front of their 'inner screen'. This distinction is controversially discussed as it depends on the task and the subject's understanding (Edquist, Rich, Brinkman, & Mattingley, 2006). Other investigations confirmed this distinction (Ward, Li, Salih, & Sagiv, 2007) and even showed anatomical differences within these subgroups (Rouw & Scholte, 2007).

In *acquired synesthesia*, subjects either could not locate the concurrent (Page et al., 1982), or they occur within the scotoma or somewhere else within the visual field (Jacobs et al., 1981). Phosphenes, in general, are located in the real world as they can be mapped within the visual field (Cowey & Walsh, 2000). And as visual concurrent are described as phosphenes, they also should be located in the real world.

In *drug-induced synesthesia*, the location of the experienced changes can be perceived with eyes open or closed. With closed eyes it is experienced on a kind of inner screen whereas with open eyes it is seen as pseudohallucinatory phenomenon in the outer world or as superimposed over real things in the outer world ('synesthetic illusions'). Principally, *drug-induced synesthesias* can be experienced in both ways, but they are more common with closed eyes (Beringer, 1927).

2.6. Inducer-concurrent characteristics

In *genuine synesthesia*, the most common pairing is between ordinal, over-learned sequences and colors (Novich et al., 2011). Most often, written days of the week are seen colored, followed in frequency by specific graphemes (letters and numbers) and months (Simner et al., 2006). Other examples include music-color (Ward, Huckstep, & Tsakanikos, 2006), music-taste (Beeli, Esslen, & Jäncke, 2005) or gustatory–lexical (Simner & Ward, 2006) synesthesia. The pairing is highly idiosyncratic to the individual, each of whom will have somewhat unique inducer-concurrent couplings (Cytowic, 2002). See Table 4 for a list of types of pairings typical to each type of synesthesia and also the homepage of Sean Day (http://home.comcast.net/~sean.day/html/types.htm) provides a comprehensive list for pairings observed in genuine synesthesia. Most synes-

Table 4
Inducer-concurrent couplings. A = acquired synesthesia, D = drug-induced synesthesia, G = genuine synesthesia. For drug-induced synesthesia see Delay et al. (1951), Leuner (1962), Masters and Houston (1966), Mayer-Gross (1931), Simpson and McKellar (1955), acquired: Afra et al. (2009), Armel and Ramachandran (1999), Jacobs et al. (1981), Jacome and Gumnit (1979), Page et al. (1982), Ro et al. (2007), genuine: Day (2004).

Inducer	Concurrent							
	Visual	Auditory	Tactile	Gustatory	Olfactory	Thermal	Body scheme/experience	Algesic
Visual	G	G	GD			D		
Auditory	GAD		GAD	G	G		D	GD
Tactile	GDA		D			D	D	D
Gustatory	GD		G		G	G		
Olfactory	GD		GD	G		G	D	
Thermal	GD		D					D
Algesic	GD		D	G	G		D	

thetes report that their mapping is unidirectional. For example, the letter 'A' may be perceived as red, but a perception of red does not evoke the letter 'A'. However, there is at least an implicit unconscious bidirectionality (Meier & Rothen, 2007). Thus, there is evidence that the inducer-concurrent coupling is bidirectional but only consciously perceived in one direction.

The concurrent and the inducer are perceived as an inseparable unitary entity (Grossenbacher & Lovelace, 2001), even though the location of inducer and concurrent may differ (see Section 2.5 about location). Through this unitary quality of the synesthetic coupling and their lifelong experience with it, synesthetes think that this kind of perception is normal and shared by everyone else. Only when they speak about it with other people do they discover that they have a special kind of perception that is never experienced by non-synesthetes (Cytowic, 2002; Emrich, Schneider, & Zedler, 2004). This shows that synesthetes are only aware of their synesthetic experience in the mirror of their society and not by the experience itself, as it accompanies them their whole life and is part of their normal perception of the world.

As synesthesia is reliably experienced, some types can prove useful (Luria, 1968; Mann, Korzenko, Carriere, & Dixon, 2009; Simner, Mayo, & Spiller, 2009; Ward, Jonas, Dienes, & Seth, 2010; Yaro & Ward, 2007). In grapheme-color synesthesia the colors can be used as a memorizing technique (Radvansky, Gibson, & McNerney, 2011; Smilek, Dixon, Cudahy, & Merikle, 2002b). For example, telephone numbers or pins can be stored through their specific color code and are retrieved by the colors. A famous example is the synesthete described by Luria (Luria, 1968) or Daniel Tammet, reciting the number Pi from memory to 22,514 digits, which both use synesthetic cues for memory retrieval. Others report that they use their synesthetic colors when searching for certain words for example in a telephone book. Richard Cytowic reports of synesthete MW who uses his taste-form synesthesia in order to season his food (Cytowic, 2002). But in general, synesthetes have no special memory skills (Rothen & Meier, 2009).

Often, synesthetes report their synesthetic experience as enjoyable and aesthetically appealing and synesthetic artists often use their synesthesia as inspiration for their artwork (for example 'Fuga' by W. Kandinsky).

With *acquired synesthesia*, auditory–visual phenomena are mostly found (Afra et al., 2009), but also other forms are possible, like auditory-tactile (Ro et al., 2007) or tactile-visual synesthesia (Armel & Ramachandran, 1999), depending on the location of brain damage.

The reported onset of visual concurrents is quite variable. It can be experienced days, weeks, or even months after the brain damage (Afra et al., 2009). The duration can also be quite variable. In some cases the synesthetic experience was persistent (Jacobs et al., 1981; Ro et al., 2007) while in others it vanished after some months (Page et al., 1982). At their initiation, the induced phosphenes can be irritating (Jacobs et al., 1981).

*M*ost often the concurrent is perceived when in a relaxed, drowsy state (Jacobs et al., 1981; Page et al., 1982). A dark environment is advantageous to elicit the phosphene (Afra et al., 2009). Also in some described cases sounds have to be unexpected or startling (Page et al., 1982).

In this form of synesthesia, the inducer and concurrent are, to some extend, perceived as simultaneous and co-occurring and often accompanied by a startle response (Jacobs et al., 1981). The reports are not quite clear about it but it can be assumed that it is basically possible to separate inducer and concurrent. For example Page et al. (1982) described the concurrent to be produced by unexpected sounds. Thus the patients seem to be aware of some sort of order in the events, one being the product of another. In addition subjects with acquired synesthesia are aware that their experience is novel as it is a new kind of perception unknown to them before the brain damage and they know that these sound and light flashes do not belong together. Otherwise they would not report it. Therefore, they recognize the synesthetic experience and are aware of them as different from other perceptions of reality (Jacobs et al., 1981).

In *drug-induced synesthesia*, a dominant mapping to the visual domain is found. In the majority of drug-induced cases, an auditory stimulation leads to visual phenomena (Shanon, 2003). Nevertheless, stimuli from all sensory domains can lead to synesthetic experiences, most typically stimuli from non-visual modalities to visual experiences, but all other combinations, even with more than one modality at once, are possible. A phenomenon found exclusively in drug-induced synesthesias is the experiencing of an altered body image that is induced by a visual, acoustical, or tactile stimulus. For example, a part of the body may morph in form and size induced by acoustical stimulation (i.e. music) (Hintzen & Passie, 2010).

Dependent on the drug used, it needs between 30 and 60 min after oral ingestion until the synesthetic experience starts (Grof, 1980; Leuner, 1962; Shulgin, 2003).

In drug-induced synesthesia subjects perceive the inducer and concurrent as an integrated unified entity. For the subjects it is even confusing to tell the single modalities apart and to state in which modality a stimulus occurs (Mayer-Gross, 1931). This phenomenon of perceived unity even goes beyond the inducer-concurrent coupling as everything seems to have a deeper sense and is connected to everything, and is the basis for often reported mystical experience (Mayer-Gross, 1931; Shanon, 2002).

The synesthetes are aware of the intoxication and the striking new (synesthetic) experiences caused by it. Persons under the influence of a hallucinogenic drug in virtually all cases remain aware that the unusual experiences which they perceive are induced by a drug and are of a temporary nature. A part of the observer ego (Scharfetter, 1980) is preserved, which Leuner called the "reflecting ego residue" (Leuner, 1962). This means that the intoxicated person is able to keep a distance to the altered experience and can consciously reflect on it.

Drug-induced synesthesias are typically experienced in a dream-like altered state of consciousness. It resembles in some respects the pre-sleep hypnagogic state (Mavromatis, 1987) but with increased vigilance (Ardis & McKellar, 1956; Leuner, 1962; Mavromatis, 1987). Some readers may discount this paralleling of the hypnagogic and the hallucinogenic drug induced state because of differences in physiological correlates, but the phenomenology and experiential features of these

states are quite similar. An environment with reduced stimuli usually leads to an increased experience of more hallucinatory and synesthetic effects because the individual is more sensitized to perception of remaining stimuli and, thereby, are more attentive to their sensations. Increases in environmental stimuli may lead to overstimulation, which sometimes can induce more as well as less hallucinatory/synesthetic effects (Kazui et al., 2009; Zubek, 1969).

The intoxicated often enjoy these kinds of experiences, similar to nearly all genuine synesthetes. Sometimes drug intoxication can lead to a change in the whole world view and personal orientation (Shanon, 2002), but these potentially personality changing effects are not related to synesthetic experiences, but are dependent on other aspects of the drug induced state (e.g. improved self-insight, mystical experiences).

The whole intoxication is characterized by a dose dependent kind of mild confusion, but usually the drug-user experiences synesthesia with a lesser or greater degree of control and is not confused but may be irritated by unusual sensory and affective sensations. Because of the hypervigilant character of the intoxication, there is no clouding of consciousness, but an irregular irritation of cognitive processing may go on. The ability for reality-testing remains intact but can in some cases be reduced or gravely altered so that even unrealistic behavior may result (Brimblecombe & Pinder, 1975).

2.7. Dynamics of synesthetic experience

In *genuine synesthesia* the concurrent appears to mimic the inducer in regard to dynamic. As language is a more stable phenomenon (letters do not move or change but are just perceived), the concurrent, i.e. color, is also not dynamic. The word is just translated into a color. An exception is music-color synesthesia as here the inducer is dynamic and also the concurrent is moving and changing (Martino & Marks, 2001).

No dynamic patterns are reported in *acquired synesthesia* (Jacobs et al., 1981; Page et al., 1982). Often the concurrents last only for a split second. The most dynamic pattern was described by Jacobs et al. (1981), where one subject described a spiraling pink kaleidoscope as a concurrent.

In *drug-induced synesthesia*, the synesthetic experience is highly dynamic. The concurrent constantly changes, and we also find feedback effects. A flow of inner experiences, integrated with the appropriate, but enhanced affectivity, is manifesting within the drug user. This flow may be altered or influenced by synesthetic phenomena, so that the dynamics of the experience are not completely altered in regard to general content or direction but can be partially influenced by the introduced synesthetic phenomena. These may even change the general course of the flow of inner experiences, but usually they are only accompanying it (Strassman, 1995). This implies that the synesthetic phenomena are an integral part of the flow of inner experiences and therefore correlate to the complexity and dynamics of the inner experience with the experiential field (Leuner, 1962; Masters & Houston, 1966).

2.8. Affectivity

In *genuine synesthesia*, the impact of affectivity is low. There are reports of touch-feeling synesthesia (Ramachandran & Brang, 2008) and emotionally mediated synesthesia (Ward, 2004), but in the dominant forms (grapheme-color/weekday-color) emotion plays virtually no role at all (but see also (Cytowic, 2002) for a different view). Most genuine synesthetes report no affective involvement of the synesthesia or an influence of their current affective state on the synesthetic experience. However there are certain types of synesthesia showing an emotional involvement, like ordinal linguistic personification (OLP), where letters have a gender and personality (Simner & Holenstein, 2007). Here the synesthetes often describe that they like or dislike some letters based on their personality. Grapheme-color synesthetes sometimes describe that they dislike letters displayed in incongruent colors (incongruent to their synesthetic colors). Or in a case of lexical–gustatory synesthesia it might be that the taste elicited by a certain word is not liked by the synesthetes. But these emotions are of secondary nature and not primarily involved in the synesthetic coupling, as here, the synesthetic coupling is evaluated emotionally as part of the normal emotional evaluation process (Damasio, 1995). Emrich et al. (2004) proposed a subtype of synesthesia called emotional synesthetes ('Gefühlssynästhetiker'). These synesthetes are characterized by a low consistency but never the less report to have synesthesia. It is proposed that the coupling is achieved over the current affective state so that the affect is depicted by the concurrent. And as our current affective state constantly changes, the inducer-concurrent pairing also changes leading to a high intrapersonal variance (low consistency).

In *acquired synesthesia* the emotional state of the synesthete does not play a role, but also some reports are available where a startle response is accompanied by a synesthetic experience. In these cases unexpected sounds trigger flashes (Page et al., 1982). Here, similar to the above mentioned exceptions, the synesthetic experience is accompanied by an emotion, but the emotion is not an integral part of the synesthetic coupling.

In *drug-induced synesthesia*, affectivity plays a central role. As Leuner states: "In general, one finds an overstimulation of affects in relation to the dose ('effect hyperthymisant,' (Divry, Bobon, & Collard, 1959))... This overstimulation 'captures' the sensory apparatus and manifests in optical, acoustic and tactile hallucinations ... the enhanced internal stimulus generation is connected with a progressive...synchronization of neighboring 'dynamic centers' and channels by lowering thresholds. Marked examples are synesthesias and the broad stream of speeding and emotionally laden associations overflooding the normal channels of the thinking process. The amplitude of the internal stimuli can no longer be conducted and consumed by the normal channels of the psychic system." (Leuner, 1968)

There are commonalities and differences of phenomenological features of genuine, acquired, and drug-induced synesthesia. In order to get a clearer picture about the different forms of synesthesia, two other points of interest are discussed next: First, what is known about how drugs influence genuine synesthesia and second what is known about the etiology of the different forms.

3. Influence of hallucinogenic drugs on genuine synesthesia

There is virtually nothing known about the impact of psychedelic drugs on genuine synesthesia. In a single case report, Mayer-Gross described a subject with genuine synesthesia who saw landscapes when listening to music (Mayer-Gross, 1931). This synesthesia gradually faded out at the age of 17. Notably, a somewhat similar synesthesia reappeared when this subject smoked psychoactive cannabis resin. With cannabis, even single tunes evoked ornaments and lines while whole pieces of music led to a known landscape for him. This is a somewhat unusual case as normally genuine synesthesias are stable and do not disappear with age.

A single sound-color synesthete interviewed by our group reported that LSD and cannabis did not increase but alter his inducer-concurrent pairings so much so that the synesthesia under the influence of the drugs was experienced by him as 'false' (a musical tone is now experienced in a wrong color). Because of dose-dependency, this effect occurs only with higher dosages. This can be interpreted as an 'overpowering' of the genuine acoustic-visual synesthesia by the drug's effects.

In another case a grapheme-color synesthete reported that she developed a new auditory–visual synesthesia pattern under LSD while her grapheme-color pairings remained unchanged. But the colors in the drug-induced form were the same as in her 'normal' synesthesia, so that the familiar experience of induction of colors expanded into the new synesthesia. The reduction of filtering of stimuli processed while under the influence of LSD created a new synesthesia that built upon a pre-existing genuine synesthesia; the individual temporarily experienced that more elements of reality induced the familiar concurrent of color production. It seems as if hallucinogenic drugs can have different, subject or synesthesia dependent, ways of influencing genuine synesthesia.

4. Etiological models

4.1. Genuine synesthesia

Genuine synesthesia is thought to be a result of 'hyper-association' between brain regions (Simner, 2012), while the exact etiology is controversially discussed. It is not clear if this 'hyper-association' is a result of a direct cross-activation of the brain areas processing the inducer and the concurrent (Ramachandran & Hubbard, 2001) or whether it is caused by feedback loops (Grossenbacher & Lovelace, 2001; Smilek, Dixon, Cudahy, & Merikle, 2001), more sensitive binding mechanisms (Emrich et al., 2004; Esterman, Verstynen, Ivry, & Robertson, 2006) or a more connected brain, in general (Hanggi, Wotruba, & Jancke, 2011). Up to now, morphological and functional neurophysiological data cannot be taken as hard evidence for one theory or the other.

The direct cross-activation theory is based on the fact that the part of the fusiform gyrus, responsible for letter detection (grapheme-area), is adjacent to area V4. The idea is that the grapheme-area has aberrant connections to V4, so that when it detects a letter, the activation is directly sent to the color center. It is assumed that these connections are due to a pruning error during childhood. Pruning is a normal process during brain development where unused connections between brain areas are removed and important, frequently used connections are strengthened. Due to a genetic aberration (Asher et al., 2009; Baron-Cohen, Burt, Smith-Laittan, Harrison, & Bolton, 1996; Hancock, 2006; Smilek, Dixon, & Merikle, 2005; Ward & Simner, 2005), this pruning may not work properly in synesthetes (Maurer & Mondloch, 2004; Spector & Maurer, 2009). The feedback theory assumes that, rather than due to aberrant connections, synesthesias are due to an unusual usage of normal connections (Grossenbacher & Lovelace, 2001). The theory is that multimodal 'higher' centers in the brain activate via feedback projections the color centers of V4. These feedback connections are present in non-synesthetes, also, but are normally inhibited. Two observations lend support to this theory. Firstly, synesthesia is context dependent. If one shows a grapheme-color synesthete a grapheme together with letters and then together with numbers, the synesthete perceive a color according to their current interpretation (Dixon et al., 2006). Thus the meaning defines the color, which points to the involvement of higher cortical areas. The other observation is that non-synesthetes can experience synesthesia during drug-intoxication, and the intoxication is not able to establish new projections (Holland, 2001).

The third etiological model focuses on the hypothetical 'binding' mechanism which is thought to be over-active in synesthetes. This is called 'hyperbinding' (Emrich et al., 2004). The binding model implies that the subjective human world is non-fragmented despite the complex parallel brain activations due to a hypothetical higher order mechanism of perceptual processing which binds together activities of different brain areas to result in a holistic perceptual world. The brain processes on which this mechanism may be based are still not known. Regarding genuine synesthesia, two types of mechanisms are implied by this model. First, studies show that the parietal cortex is involved in synesthetic perception, as disruption of the parietal cortex with transcranial magnetic stimulation (TMS) inhibits the synesthetic Stroop effect (Muggleton, Tsakanikos, Walsh, & Ward, 2007; Esterman et al., 2006). In other words, the parietal cortex appears responsible for the unusual binding in synesthetes. The other mechanism involves the limbic system, which is hypothesized to ''bridge' the inducer

and concurrent. According to this model, which is called the "model of the limbic bridge" (Emrich et al., 2004), the coupling of sensory perception through synesthesia is caused by a bridging by the limbic system between different brain areas. The idea is that sensory information is evaluated emotionally by the limbic system, and, when sensory data appears to have the same emotional "rating," they are bound together by a "limbic bridge." This hypothetical "limbic validating connecting link" connects the sensual percept with emotions and the accompanying brain activity that produces the synesthetic coupling (Emrich et al., 2004). This idea was initially suggested by R. Cytowic, who observed limbic activations in synesthetes using scintigraphic brain imaging techniques (Cytowic, 2002; Cytowic & Stump, 1985). Due to the observation that a subpopulation of synesthetes exhibited genuine synesthetic coupling as well as induction of synesthesia by emotions, the 'limbic binding' hypothesis posits limbic co-activations of sensory inputs to which 'binding' phenomena are realized. This hypothesis is also in line with the neurological brain hypothesis by Damasio (Damasio, 1995).

Neurophysiological data on synesthesia offer a rather heterogeneous set of explanations. Differences between synesthetes and controls can be detected at the early stages in processing of visual or acoustical data streams (Barnett et al., 2008; Goller, Otten, & Ward, 2009). Some studies show that grapheme-color synesthetes have an unusual activation of the color center in V4 (Hubbard, Arman, Ramachandran, & Boynton, 2005; Nunn et al., 2002; Sperling, Prvulovic, Linden, Singer, & Stirn, 2006) and also appear to possess a larger V4 area (Jancke, Beeli, Eulig, & Hanggi, 2009). V4 and a part of the fusiform gyrus are simultaneously activated during letter processing in synesthesia (Brang, Hubbard, Coulson, Huang, & Ramachandran, 2010). Nevertheless, other authors claim that V4 is not involved in synesthetic perception (Hupe, Bordier, & Dojat, 2011).

The fusiform gyrus, with partial responsibility for letter detection (James et al., 2004), seems to be larger (Weiss & Fink, 2009) and more connected (Rouw & Scholte, 2007). There is also frontal lobe involvement in synesthesia with activation found within the inferior frontal (Sperling et al., 2006) and left frontal (Rouw & Scholte, 2007) cortex. Involvement of the inferior temporal cortex also occurs (Paulesu et al., 1995; Sperling et al., 2006). Different studies have also found activation of parietal cortex in synesthesia (Neufeld et al., 2011; van Leeuwen, Petersson, & Hagoort, 2010; Weiss, Zilles, & Fink, 2005). Rouw and Scholte (2007) found increased structural connectivity in the left superior parietal cortex with diffusion tensor imaging (DTI), and Weiss and Fink (2009) found morphological changes in the intraparietal sulcus with voxel-based morphometry (VBM). Thus, while many differences are observed in the brains of synesthetes compared to non-synesthetes, the current data is not able to falsify one of these models. A major problem responsible for some of these inconsistencies might be individual differences between various subtypes of genuine synesthetes as well as synesthetic individuals (Hubbard et al., 2005). For example, researchers found structural (Rouw & Scholte, 2010) and functional (van Leeuwen, den Ouden, & Hagoort, 2011) differences between the brains of projector and associator synesthetes. The research suggests that parietal mechanisms are important for synesthetic perception and that the degree of V4 activation depends on the specific type of synesthete (Hubbard, 2007; Rouw, Scholte, & Colizoli, 2011).

4.2. Acquired synesthesia

Localized brain damage is responsible for acquired synesthesia. In particular, it is assumed that synesthetic perception arises due to neuroplastic changes that occur after brain damage (Ro et al., 2007; Ward, 2007). Neuroplasticity is the experience dependent change of function and structure of the organization of the brain (Buonomano & Merzenich, 1998; Merzenich et al., 1983). In case of acquired brain damage the whole communication pattern between neurons changes, as some areas are not working any more. This new usage in turn leads to a reorganization of the brain which can produce synesthetic experience. It should also be noted that it is also possible that loss of sensory input decreases thalamic activity, which then leads to an unmasking of pre-existing pathways. The exact coupling in acquired synesthesia depends on the damaged brain areas. The interested reader is referred to Afra et al. (2009) for further information. Even though the exact mechanism leading to acquired synesthesia is not known, most researches agree that it is due to morphological changes in the brain.

4.3. Drug-induced synesthesia

There are no explicit theoretical models for drug-induced synesthetic phenomena. Nevertheless, the psychological and sensory alterations induced by hallucinogenic drugs are based on discrete psychophysiological and neurophysiological changes. A discussion of those changes may provide some ideas about the etiology of hallucinogen-induced synesthesia. In general, hallucinogens appear to preferentially inhibit serotonergic neuron transduction while sparing postsynaptic serotonergic receptors from upregulating/downregulating. This preference is shared in a somewhat limited fashion by non-indol hallucinogens. Non-hallucinogenic analogs of LSD show no such preference. Most hallucinogens modify activity in two areas: the locus coeruleus (LC) and pyramidal cells in the cortex (Aghajanian & Marek, 1999).

Serotonin (5-hydroxytryptophan; 5-HT) is produced by a small number of neurons (1000s) that each innervates as many as 500,000 other neurons. For the most part, serotonin neurons originate in the raphne nuclei (RN) of the midbrain. One major group of these is the LC, which controls the release of norepinephrine, a neurotransmitter important for the regulation of the sympathetic nervous system. The LC also has neurons that extend into the cerebellum, thalamus, hypothalamus, cerebral cortex, and hippocampus. The RN extends its projections into the brainstem and up into the higher cortex. It has been suggested that neurons of the RN may inhibit sensation, thus protecting the brain from sensory overload. The fact that the LC and RN innervate virtually every part of the brain shows that a relatively small area can impact large projections (Passie, Halpern, Stichtenoth, Emrich, & Hintzen, 2008).

In general, 5-HT may be labeled a primarily inhibitory neurotransmitter. Thus, when its activity is decreased, the next neuron in the chain is freed from inhibition and becomes more active (similar to disinhibited feedback models of genuine synesthesia). However, a few 5-HT receptors are excitatory ion channels (5-HT_3), and some 5-HT subtypes may have excitatory effects depending upon the G protein coupling within specific neurons. Since serotonergic systems appear to be intimately involved in the control of sensation, sleep, attention, and mood, it may be possible to explain the actions of LSD and other hallucinogens by their disinhibition of these critical systems. It is important to note that serotonin agonists alone do not cause the hallucinations seen in LSD intoxication (Aghajanian & Marek, 1999; Glennon, 1990; Hüther & Rüther, 2000). The interested reader is referred to Hintzen and Passie (2010) for further information.

It was initially hypothesized that drug-induced altered states of consciousness can be conceptualized as complex disturbances arising from more elementary deficits of sensory information in cortico-striato-thalamico-cortical feedback loops. These disturbances lead to a disruption beyond the normal range of thalamic gating of sensory and cognitive information and results in an overloading inundation of the cortex. This disruption is achieved over the cortico-striato-thalamic pathway, which can be modulated via the mesostriatal serotonergic pathway described above (Vollenweider & Geyer, 2001).

More recently, other researchers found no consistent thalamic activation from hallucinogens (Gouzoulis-Mayfrank et al., 1999; Riba et al., 2006). Vollenweider himself (2009, personal communication) questioned conclusions of his former scientific hypothesis and pointed out that frontal and paralimbic brain activation most probably results from direct influences of hallucinogens on pyramidal neurons in the cortex and other populations of neurons in paralimbic structures.

Another theory states, similar to the disinhibited feedback model, that the effects of drug intoxication are due to strong activation of a brain region, which then spreads to neighboring areas that, in turn, lead to the found effects (Leuner, 1968, 1981). Neuroimaging studies show activation of frontal, limbic, and paralimbic structures by the major hallucinogens (Gouzoulis-Mayfrank et al., 1999; Riba et al., 2006; Vollenweider et al., 1997). There is also an increase in cortical excitability, mainly induced by direct agonistic effects on 5-HT_{2A} receptors located on cortical pyramidal neurons (Nichols, 2004).

Yet is there a different point of origination for simple versus complex forms of visual (potentially synesthetic) imagery? Zador (1930) experimented with subjects with disturbances at different parts of the visual system. He demonstrated that the more primitive, entoptic phenomena (stars, circles, flashes, etc.) can be found only on the side where the eye is still intact. In contrast, complex scenic phenomena were perceived on an ''inner screen,'' even when vision from both eyes was completely lost (Zador, 1930). This suggests that the visualized phenomena originate within the brain itself. This view is also supported by new neuroimaging data generated from studying the effects of the hallucinogenic drug dimethyltryptamine on the visual systems of the brain (de Araujo et al., 2011). Additionally, it was found that more simple visual phenomena are not accompanied by emotions, but the more complex visual phenomena are typically integrated with intense emotions.

Table 5
Comparison of phenomenological features of the different types of synesthesia.

	Genuine synesthesia	Acquired synesthesia	Drug-induced synesthesia
Automaticity	Yes	No	No
Controllability	No	No	Dose dependent
Consistency	Constant couplings	Inconstant	Inconstant coupling
Interpersonal variance	High	Lower	High
Intrapersonal variance	Low	Low	High
Changes of external world perceptions	No	No	Yes (Illusions, pseudo-hallucinations)
Location of concurrent	Projector versus associator	Not reported, phosphene- like	Predominant in front of inner eye
Inducers	Nearly every external stimulus possible; often language /linear sequence related inducer	Unspecific tone related	Unspecific tone-related
Useful	Often	No	Maybe for enjoying the experience
Vigilance	Independent of arousal	Arousal dependent	Arousal dependent
Optimal environmental condition for appearance	None	Dark room reduction of environmental stimuli	Dark room reduction of distracting environmental stimuli
State of consciousness	No altered state, Normal vigilance	Often during decreased arousal (relaxed/still/drowsy, dark room)	Hypnagogic like, but with increased vigilance
Complexity	Simple (geometrical) forms often with color	Simple forms (phosphenes/ photism)	Simple colored forms to complex colored scenes
Type of inducer	Sensory and conceptually driven	Sensory driven	Sensory driven
Meaning	Dependent on interpretation	Independent on interpretation	Independent on interpretation
Synesthesia as part of the steady flow of altered inner experience	No	No	Yes

Table 6
Comparison of neurophysiological models of different forms of synesthesia.

	Genuine synesthesia	Acquired synesthesia	Drug-induced synesthesia
Alterations of hemispheric laterality	Unknown	Unknown	Right hemispheric activation
Thalamic changes	Unknown	Neuronal rewiring by neuroplastic processes	Functional activity increased
Cortical involvement hardwiring	Hardwiring of synesthesia capacity possible; debate open	Hardwiring altered Lesion dependent	No hardwiring changes
Cortical involvement functional	Increased frontal, parietal, temporal, occipital (V4) cortical activation (type dependent)	Lesion dependent	Increased global cortical activation
Bidirectional	Implicit (Meier & Rothen, 2007)	Unclear	Some
Serotonin	Suggested: 5HT-S_{2a} as 'synesthesia receptor' as inhibition decrease synesthesia (Brang & Ramachandran, 2008)	No evidence	5-HT 2_A and 5-HT 1_C activation (with 5HT-2_A blocking: decrease of synesthesias reported)

5. Discussion

Within the scientific literature about genuine synesthesia, very few authors discuss about drug-induced synesthesia, especially in comparison to genuine synesthesia (Cytowic, 2002; Grossenbacher & Lovelace, 2001; Hubbard & Ramachandran, 2003; Shanon, 2003). These discussions mention the phenomenon, but there is no coherent and conclusive assessment. Nevertheless, studies of drug-induced synesthesia are regularly used for the interpretation and etiological models of genuine synesthesia. Especially in the inhibitory feedback model, it is stated that genuine synesthesia cannot be caused by aberrant connections because hallucinogenic drugs are potentially able to induce synesthesia.

When comparing the different forms of synesthesia, more differences than commonalities are observed. Phenomenological findings are summarized in Table 5 and etiological findings are summarized in Table 6.

Independent of the form of synesthesia, nearly all synesthetic couplings occur between the visual and the auditory domain, while genuine synesthetes have the most specialized couplings. These modalities are not distributed equally. It is striking, that acoustical stimuli play a major role as inducer while only a few synesthetes have acoustical concurrents (Hubbard & Ramachandran, 2003; Saenz & Koch, 2008; Shanon, 2003). The concurrents, in fact, are mostly visual, i.e. color and forms. It is also notable that during hallucinogen induced states acoustical hallucinations are also rarely observed, while visual hallucinations are quite common. Early on, Mayer-Gross (1931) speculated that the acoustical modality is less prone to intoxication, i.e. less susceptible to functional changes. This might be due to the fact that, when comparing visual and acoustical processing, much more of the brain is allocated for visual processing. In monkeys, roughly 50% of the neocortex is engaged in visual processing while only about 3% is devoted to acoustical processing (Kandel et al., 2000). Another reason could be that the acoustical information is more preprocessed before entering the neocortex. While visual information travels from the retina via the lateral geniculate nucleus to the primary visual cortex, acoustical information travels from the cochlea via the superior olivary nucleus, inferior colliculus and the mediate geniculate body to primary auditory cortex (Kandel et al., 2000). A lot of processing of acoustical stimuli is already done in the brainstem and deep thalamic nuclei.

Comparing the concurrents one observes mainly simple flashes in acquired forms whereas more elaborated visual effects (like colored letters) are found in the genuine forms. Drug-induced synesthesia can be even more complex and is highly dynamic. In drug-induced forms, the visual concurrent is mainly modulated by the affective state of the intoxicated person and the inducer has more global effects. Also, different types of synesthesia are found in the drug-induced form. First we find the 'normal' case where the inducer activates the concurrent. But also one modality can influence another rather than creating a new dimension of synesthesia. In other words, the inducer modulates the concurrent in drug-induced synesthesia. While a hallucinogen user may hallucinate some visual spiral, the spiral will begin to change with music. This modulatory subtype is exclusively found in drug-induced synesthesia.

When looking at consistency, differences between drug-induced and genuine synesthesia became clear. Genuine synesthesia is consistent, automatic and independent of the subject's current sensorium, whereas the drug-induced and acquired forms are inconsistent, not automatic and highly dependent on the current state of the subject.

In regard to the synesthetic experience itself, it is evident that the drug-induced synesthesias are much more intense and dynamic as well as flexible compared to drug-free acquired synesthetic experiences. The emotional involvement in the drug-induced synesthetic experience is also greater than with the other forms. The drug-induced synesthetic experience is a much more pronounced and impressive subjective experience than with the more selective sensory alteration experiences in genuine and acquired forms. In drug-induced synesthesia, the experiences are embedded in a much broader flow of powerfully altered subjective experiences, especially within the visual domain (illusion, pseudo-hallucinations and visionary experiences).

In short, even though drug-induced and genuine forms of synesthesia share some superficial commonalities, it looks like different mechanisms are responsible for each as there are fundamental differences. This could be explained with functional

changes through the drugs effects and morphological changes in the acquired forms. Genuine forms appear not to fit into either scheme.

6. Bottom-up and top-down processing in synesthesia

Drug-induced synesthesias are perhaps best understood as examples of the enhancement of bottom-up processes. Higher level cognitive processing exerts only a minor influence on drug-induced synesthetic perception. In genuine synesthesia, on the other hand, top-down processes appear to play a major role, as here conceptualization is definitely involved (Bargary et al., 2009; Dixon et al., 2006; Smilek, Dixon, Cudahy, & Merikle, 2002a). In grapheme-color synesthesia, it is necessary that the synesthete interprets the stimuli as letters, so grapheme-color is only triggered when the concept of letters is activated: clearly, higher level concept related processes are involved. It seems that genuine synesthesia is more about concept formation than sensory processing. The question is then, why this happens. As one finds most of the inducers to be of quite abstract nature, synesthesia might be a kind of (unconscious) compensatory strategy to concretize abstract entities in order to better cope with them. Such a conceptualization effect is not known in drug-induced synesthesia, which appears to be a more direct coupling of sensory information insofar as drug-induced synesthesia appears to be independent of top-down processes.

7. Conclusions

We examined the three types of synesthesia (genuine, acquired and drug-induced). This paper presents evidence that there are many more differences than similarities.

This is especially true in regards to most phenomenological features as well as in how they are subjectively experienced. Indeed, it appears that there is only one basic feature common to all types, and that is the simultaneous co-activation of different senses.

In regard to their specific features and the models proposed for their etiology, we recommend placing drug-induced synesthesias in a separate category. Nevertheless, synesthesias should be studied more explicitly in drug studies, which seem to be a neglected topic up to now, even in spite of their impressive nature. We do not think that the study of drug-induced synesthesias will lead to great insights into genuine synesthesia, because of the significant differences between these forms.

Concerning genuine synesthesia, one can infer how capable the different neuronal mechanisms are for production of synesthetic perceptions. Mere rewiring processes as seen in acquired forms are not able to elicit the whole range of phenomenological features seen in genuine forms. Functional changes, on the other hand, as seen in drug-induced forms, induce much stronger changes.

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