

SNARE complex in developmental psychiatry: neurotransmitter exocytosis and beyond

Renata Basso Cupertino¹ · Djenifer B. Kappel¹ · Cibele Edom Bandeira¹ ·
Jaqueline Bohrer Schuch¹ · Bruna Santos da Silva¹ · Diana Müller¹ ·
Claiton Henrique Dotto Bau¹ · Nina Roth Mota¹

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Abstract Multiple biological processes throughout development require intracellular vesicular trafficking, where the SNARE (soluble *N*-ethylmaleimide-sensitive factor (NSF) attachment protein (SNAP) receptors) complex plays a major role. The core proteins forming the SNARE complex are SNAP-25 (synaptosomal-associated protein 25), VAMP (vesicle-associated membrane protein) and Syntaxins, besides its regulatory proteins, such as Synaptotagmin. Genes encoding these proteins (*SNAP25*, *VAMP1*, *VAMP2*, *STX1A*, *SYT1* and *SYT2*) have been studied in relation to psychiatric disorders susceptibility. Here, we review physiological aspects of SNARE complex and genetic association results reported for attention deficit hyperactivity disorder, both in children and adults, autism spectrum disorders, major depressive disorder, bipolar disorder and schizophrenia. Moreover, we included findings from expression, pharmacogenetics and animal model studies regarding these clinical phenotypes. The overall scenario depicted here suggests that the SNARE complex may exert distinct roles throughout development, with age-specific effects of genetic variants in psychiatric disorders. Such perspective should be considered in future studies regarding SNARE complex genes.

Keywords SNARE · Development · Psychiatry disorders · ADHD · DEVELOPM.PSYCH

Introduction

SNARE (soluble *N*-ethylmaleimide-sensitive factor (NSF) attachment protein receptors) complex is a large family of proteins that plays a major role in intracellular vesicular trafficking in eukaryotic cells. Such process is essential in different biological events, such as cell division, maintenance of subcellular compartments, protein and hormone secretion and neurotransmitter release (Zylbersztejn and Galli 2011). The SNARE complex is formed by members of the SNAP-25 (Synaptosomal-Associated Protein 25), VAMP (Vesicle-Associated Membrane Protein) and Syntaxins families. These proteins interact creating a four-helix bundle, formed by two helices of SNAP-25, one vesicle-transmembrane VAMP and one presynaptic plasma membrane Syntaxin that approximates the vesicle and plasmatic membranes (Sutton et al. 1998; Brunger 2000) (Fig. 1). Other proteins interact with the SNARE complex and regulate it, such as Munc-18, Complexin, Synaptophysin and the better studied Syt (Synaptotagmin) (Südhof 2013).

According to cell tissue and developmental stage, distinct family members of SNARE complex present different expression profiles. SNAP-25 family members are characterized by the presence of two SNARE domains, which are the binding sites between SNAP-25 and VAMP and Syntaxin SNARE domains, in order to form the core SNARE complex. The most studied member of this protein family is SNAP-25, which is expressed in neurons and directly involved in neurotransmitter release. It is anchored to the presynaptic plasma membrane through palmitoylation of cysteine

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✉ Claiton Henrique Dotto Bau
claiton.bau@ufrgs.br

¹ Department of Genetics, Instituto de Biociências—
Universidade Federal do Rio Grande do Sul, Avenida Bento
Gonçalves, 9500, Porto Alegre, RS CEP 91501-970, Brazil

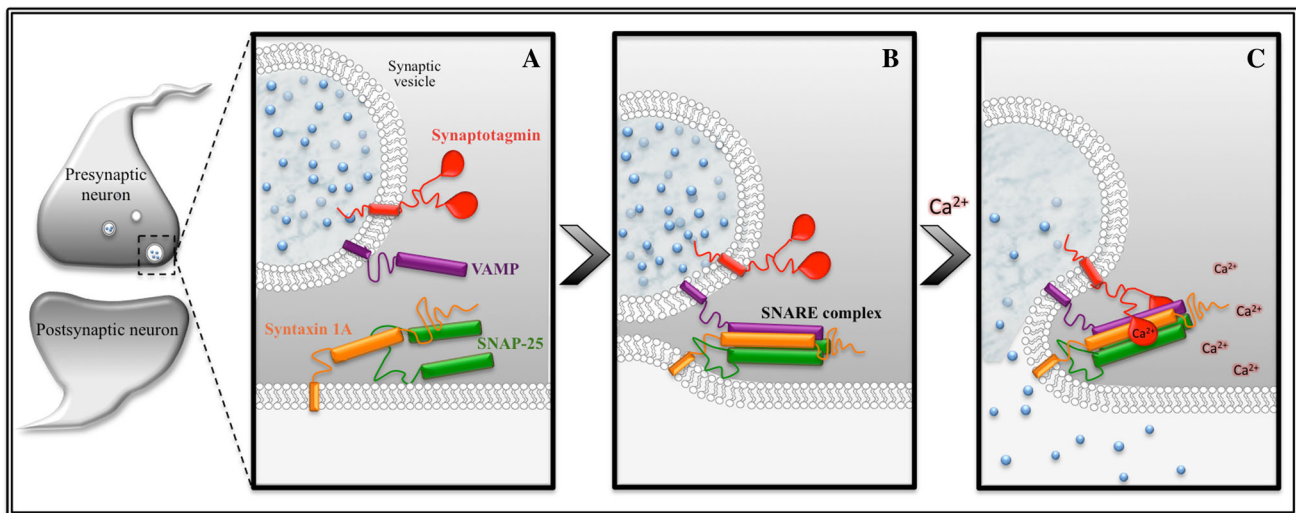


Fig. 1 SNARE complex assembly at the presynaptic terminal allowing neurotransmitter release. **a** Components of the core SNARE complex—SNAP-25 (green), Syntaxin 1A (orange) and VAMP (-1 or -2) (purple) -, as well as the regulatory protein Synaptotagmin (I or II) (red), are shown individually. **b** Assembly of the core SNARE complex, approximating plasma and vesicle membranes; the cytoplasmic SNAP-25 forms a heterodimer with Syntaxin 1A through the binding of SNARE domains (represented by the rectangles). Next, VAMP (-1 or -2) binds to the second SNARE domain of SNAP-25

forming a parallel four-helix bundle. *Squares* represent plasma (for Syntaxin-1A) and vesicle (for VAMP and Synaptotagmin) transmembrane domains. The SNARE complex is completely assembled. **c** Upon Calcium (Ca^{2+}) influx, plasma and vesicle membranes are joined and fusion pore is opened through the binding of Ca^{2+} to the two calcium-binding domains (red balloons) of Synaptotagmin, allowing neurotransmitter release (blue dots). Other regulatory proteins involved in the process are not shown

residues. SNAP-25 paralogs, such as SNAP-23, -29, -47, present slightly different properties, and although they may also be expressed in the brain in a distinct distribution (Ravichandran et al. 1996; Steegmaier et al. 1998; Holt et al. 2006; Yamamori et al. 2011), their genetic variants are far less studied. The VAMP family is comprised by 7 proteins that are involved in vesicle fusion (VAMP-1/Synaptobrevin 1, VAMP-2/Synaptobrevin 2, VAMP-3/Cellubrevin, VAMP-4, VAMP-5/Myobrevin, VAMP-7/Ti-VAMP, VAMP-8/Endobrevin) (Larra and Khan 2014). They are characterized by one SNARE domain and one C-terminal transmembrane domain. VAMP-1 and -2 are expressed in the synaptic vesicles of neurons and secretory granules of endocrine and exocrine cells (Trimble 1993). In humans, the Syntaxins family is composed by 16 members (Syntaxin-1A, -1B, -2, -3, -4, -5, -6, -7, -8, -10, -11, -12, -16, -17, -18 and -19). Among them, Syntaxin-1A, -1B and -3 are expressed at presynaptic nerve terminals and involved in synchronous neurotransmitter release, possibly acting on vesicle docking (Ullrich et al. 2015). While Syntaxin-1A and 1B are the major Syntaxin isoforms in brain, Syntaxin 3, for example, is most important for retinal exocytosis (Curtis et al. 2010). They are characterized by a single SNARE domain, a C-terminal transmembrane domain and an N-terminal regulatory domain (Teng et al. 2001). Furthermore, an important family of proteins that interacts with the SNARE complex is the Syt family, which consists of 17 members (SytI to

SytXVII), characterized by an N-terminal intravesicular domain, a transmembrane domain and two C-terminal calcium-binding C2-domains (Ullrich et al. 1994; Südhof 2002). It has been shown that SytI, -II and -IX play a critical role in fast Ca^{2+} triggered exocytosis, which is essential for appropriate neurotransmission (Geppert et al. 1994; Sun et al. 2007; Xu et al. 2007). These three members of Syt family are differentially expressed in the brain, which confer distinct release properties. It has been described that SytII promotes the fastest synapse (Xu et al. 2007), which is consistent with its major localization in neurons mediating auditory circuits (Xiao et al. 2010), while SytIX is the slowest and it is located predominantly in the striatum and limbic system, mediating emotional responses. SytI is slightly slower than SytII and it is equally distributed in all forebrain regions (Xu et al. 2007).

On the following sections we will focus on functional characteristics of specific members of the core SNARE complex (SNAP-25, VAMP-1/-2 and Syntaxin 1A) that mediate neuronal exocytosis (e.g. neurotransmitter release and growth of neuronal membranes), as well as on the most studied regulatory protein (Syt) occurring on neuronal surfaces. We also review the role of their genetic variants on the susceptibility to five major psychiatric disorders: Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorders (ASD), Major Depressive Disorder, Bipolar Disorder and Schizophrenia. The role of other

regulatory and/or less studied SNARE proteins will not be discussed.

SNARE proteins and its multiple biological functions

SNARE proteins are involved in biological processes throughout several stages of the development, from fertilization to neural development and synaptic plasticity, and even during adulthood and aging (Hepp and Langley 2001). The first stage of the development could be considered the fertilization process itself, where SNARE proteins participate in the main membrane fusion events: acrosomal exocytosis (De Blas et al. 2005) and fusion of male and female gametes (Gadella and Evans 2011). Additionally, following gametes fusion, the SNARE complex acts on cortical reaction (granules exocytosis), an essential process in order to avoid polyspermic fertilization (Gadella and Evans 2011). Moreover, studies focusing on the Syntaxins family have demonstrated that it also mediates essential cell fusion and division events during early embryogenesis in *Drosophila* (Burgess et al. 1997), in the two-cell stage of sea urchin (Conner and Wessel 1999) and in plants (Touihri et al. 2011). Supporting an essential role of Syntaxins in embryogenesis, knockout mice of *Stx1a* showed that most of *Stx1a*^(-/-) die in utero having a reduced body size and abnormal development (McRory et al. 2008). Furthermore, a recent study has also suggested that Syntaxin-1A influences the sexual maturity and egg size in *Locusta migratoria* (Chen et al. 2015).

The nervous system development also requires SNARE proteins. It has been suggested that SNAP-25 may be involved in neurite sprouting (Shirasu et al. 2000; Kimura et al. 2003) and elongation (Osen-Sand et al. 1993), whereas VAMP-2 might promote neurite elongation (Shirasu et al. 2000; Kimura et al. 2003) and Syntaxin-1A could be related to axonal growth (Igarashi et al. 1996) and neurite sprouting as well (Yamaguchi et al. 1996). SNARE-regulatory proteins also seem to participate in the neural development, as demonstrated by the involvement of Syt1 and Syt2 in promoting neurite outgrowth in in vitro studies conducted with rat adrenal pheochromocytoma PC12 cell line, a well-established cellular model used in studies of neuronal function and development (Fukuda et al. 2002). Furthermore, Syt1 might also be involved in axon branching, as reported by a study with cultured chicken forebrain neurons (Greif et al. 2013). Moreover, the expression of SNARE proteins changes throughout life stages suggesting a different role of these proteins during development. For example, experiments with rats demonstrated that Vamp has very low expression levels in the prenatal period, increasing after birth until adulthood; while Syntaxins are highly expressed in the prenatal period

and in a short period after birth, decreasing rapidly and then maintaining a constant baseline level (Shimohama et al. 1998). SNAP-25 seems to have an important role in synaptogenesis, since animal studies have shown that Snap-25 is highly expressed in early postnatal maturing rat brains and it shifts its subcellular localization from axons and cell bodies to presynaptic terminals in adults (Oyler et al. 1991).

Moreover, to evaluate the SNAP-25 function, Hess et al. (1992) used mutant mice with a deletion on the distal portion of chromosome 2, which encompasses the *Snap25* gene. This animal model is known as *Coloboma* mouse and was described for the first time in 1964 by Dr. Margaret Dickie in the Jackson Laboratory (Theiler et al. 1978). The homozygous deletion was shown to be lethal, leading to the animal's death during the embryonic period. Experiments with heterozygous *Coloboma* mice demonstrated that they had a 50 % decrease on the *Snap25* mRNA and protein levels, without affecting its normal tissue distribution profile. These mice also presented small eyes due to a failure in separating cornea and lens epithelium during eye development. Additionally, they displayed head bobbing and locomotor hyperactivity (Hess et al. 1992). It has been strongly suggested that the lack of *Snap25* in *Coloboma* mice is implicated on this hyperactive phenotype since a *Snap25* transgene insertion normalizes locomotor activity levels (Hess et al. 1996). Further studies with *Coloboma* mice reported delayed achievement of neurodevelopmental milestones, such as righting reflex and motor coordination (Heyser et al. 1995) and an abnormal presynaptic catecholamine regulation (Jones et al. 2001).

SNARE proteins are also essential for neuronal maintenance. It has been demonstrated that SNAP-25 and Syntaxin-1 are directly required for neuronal survival as they are responsible for the recycling of proteins on plasma membrane surface (Peng et al. 2013). Further Syntaxin-1 studies with animal model indicated that Stx1b seems to be the most involved in neuronal survival and development (Kofuji et al. 2014; Wu et al. 2015). SNARE proteins seem also to participate in the Brain-Derived Neurotrophic Factor (BDNF) secretion, which is a hormone that regulates neuronal development and plasticity (Shimojo et al. 2015).

The SNARE complex might also have a function on behavioral response. For example, Stx1a is involved in abnormal behavioral response in mice possibly due to dysregulation in the hypothalamic-pituitary adrenal axis response (Fujiwara et al. 2011), reinforcing the role of Stx1a in the hormone regulation during life events. This system plays a central role in modulating response to stimuli and has been implicated with abnormal development and psychiatric disorders (Caspi et al. 2003; Jiang et al. 2009; Bortoluzzi et al. 2015; Roberts et al. 2015).

Additionally, a rare human variant in *SYT1* gene (I368T) has been recently described in a case-report as implicated with severe behavioral impairments and cognitive deficits (Baker et al. 2015).

Concerning the role of SNARE proteins during aging, studies have demonstrated that SNAP-25 is necessary for cognitive functioning (Gosso et al. 2006) and long-term memory consolidation (Hou et al. 2004; 2006). A non-pathological age-dependent cognitive decline is observed in humans, yet little is known about the neurobiological processes underlying such decline. Observing hippocampal protein expression levels from rats at different ages, Vanguilder et al. (2010) demonstrated a significant decrease in a large subset of proteins involved with neurotransmitter release between adulthood and advanced-age stage, including Snap-25, Vamp-2, Syntaxin-1, Syt1 and Synaptophysin. The hippocampus is responsible for learning and memory consolidation, therefore both functions could be impaired by the reduced expression of proteins involved in neurotransmitter release. In fact, there is evidence that reduced Synaptophysin expression in hippocampus is related to impaired spatial learning (Smith et al. 2000) and memory decline (Bennett et al. 2006) with aging.

Post-translational modifications of SNARE proteins

Palmitoylation is an important post-translational modification in SNARE proteins that is essential to regulation and their correct attachment in the membrane (el-Husseini Ael-D and Bredt 2002; Greaves and Chamberlain 2007). Most of SNARE proteins are palmitoylated in adult brain (Veit et al. 1996, 2000; Lane and Liu 1997; Vogel and Roche 1999; Kang et al. 2004). For example, SNAP-25 has a rich-cysteine domain wherein one or more cysteines are palmitoylated and this is essential for the plasma membrane targeting (Veit et al. 1996; Gonelle-Gispert et al. 2000). Studies with embryonic rat brains showed that in this early stage Syt1 and Vamp-2 lack this post-translational modification. This different palmitoylation profile in embryonic cells indicates that it could be developmentally regulated, influencing SNARE function across life stages (Veit et al. 2000). For example, it has been suggested that Syt1 palmitoylation might affect its interaction with other proteins and specific microdomains of the presynaptic membrane (Prescott et al. 2009). Moreover, dysregulated palmitoylation has been implicated in a number of psychiatric phenotypes, such as Schizophrenia and Intellectual Disability (Young et al. 2012).

Protein phosphorylation is another important post-translational mechanism for regulating synaptic activity. It has been shown that Cyclic AMP-dependent Protein Kinase A and Casein Kinase II can phosphorylate SNAP-25 and Syntaxin-1A, respectively (Risinger and Bennett

1999). Although phosphorylation itself has minimal effects on the in vitro assembly of the SNARE complex, it was demonstrated that it enhances the interaction between Syntaxin-1A and SytI (Risinger and Bennett 1999). SNAP-25 is also phosphorylated by Protein Kinase C (Nagy et al. 2002) and such mechanism might affect the modulation of neuronal voltage-gated calcium channels (Pozzi et al. 2008) and seems to improve fast exocytosis triggering by recruiting secretory vesicles to the plasma membrane (Nagy et al. 2002). Furthermore, Snap-25 phosphorylation is dynamically regulated by stress in stress-related regions in mouse brain, such as cerebral cortex, hippocampus and amygdala (Yamamori et al. 2014). Mice with sleep deprivation, for example, which are animal models of mania, exhibited increased levels of phosphorylated Snap-25 in the hippocampus and prefrontal cortex (Abrial et al. 2015). Another study with animal models demonstrated that when Snap-25 could not be correctly phosphorylated due to a homozygous mutation, mice showed strong anxiety-related behavior, convulsive seizures and lower serotonin and dopamine levels in the amygdala (Kataoka et al. 2011). Additionally, another post-translational modification that has recently been described is the SUMOylation in Syntaxin-1A. It is essential to appropriate temporal and spatial regulation of neurotransmitter release and synaptic function, where the SUMOylation leads to a decreased affinity of Syntaxin-1A to other SNARE proteins and influence the balance of synaptic vesicle endo/exocytosis, increasing the endocytosis (vesicle recycle) (Craig et al. 2015).

Distinct expression profiles among isoforms and family members

Distinct isoforms of SNARE proteins have been shown to display temporal differences in expression profiles. SNAP-25 has two main isoforms, SNAP-25a and SNAP-25b, which are generated by alternative splicing of the mutually exclusive duplicated exon 5 (5a and 5b) and differ by only 9 of the 39 amino acids from this exon (Bark 1993). Such duplication of exon 5 occurred more than 400 million years ago, during early bony fish development, in which sensory and motor systems were well developed (Johansson et al. 2008). Different from what was initially thought, the functional difference between SNAP-25a and SNAP-25b seems to be due to two nonconservative substitutions at the first SNAP-25 SNARE domain, and not due to the different localization of one palmitoylated cysteine (Nagy et al. 2005).

The relative expression levels of the two isoforms in rat brain drastically changes between embryogenesis and postnatal period; Snap-25a is the main isoform expressed in mouse brain in embryonic stage but 2 weeks after birth, Snap-25b becomes the major splice variant and later in

adulthood this isoform represents more than 90 % of total SNAP-25 expressed in the brain (Bark et al. 1995; Boschert et al. 1996). This switch between major isoforms throughout development suggests that SNAP-25a may participate mainly in axonal growth, while SNAP-25b could be primarily associated with fast neurotransmitter release. Snap-25b seems to be better than Snap-25a in priming synaptic vesicles, a key step for efficient exocytosis (Sørensen et al. 2003), thus supporting a more prominent role of Snap-25b in neurotransmission.

There are also spatial differences between the isoforms expression profiles during adulthood. Although most brain regions express mainly Snap-25b, in the pituitary gland the Snap-25a remains as the major isoform (Bark et al. 1995; Prescott and Chamberlain 2011). In humans, a post-mortem study showed similar pattern of results, in which SNAP-25b was the most expressed isoform in almost all adult brain areas (Prescott and Chamberlain 2011). Experiments with mutant mice demonstrated that animals without Snap-25b showed developmental anomalies, spontaneous seizures, and impaired short-term synaptic plasticity (Johansson et al. 2008). Moreover, adult mutants had morphological changes in the hippocampus with a severe impairment of spatial learning, supporting the importance of this duplication to enhanced functional plasticity in higher eukaryotes (Johansson et al. 2008).

What leads to this expression switch between the SNAP-25 isoforms remains unclear. It has been suggested that electrical activity could be responsible for such isoform expression profile changes, based on evidences that chronic depolarization induces the Snap-25b expression on PC12 cells, which would be expressing Snap-25a under normal culture conditions (Hepp et al. 2001). Other factors might also influence this process since in adult brain regions involved with more plasticity (olfactory bulb, hippocampus, pineal gland, substantia nigra/pars compacta), Snap-25a and Snap-25b are almost equally expressed in rat brain (Boschert et al. 1996). In this sense, it has been suggested that growth factors, such as Nerve Growth Factor (NGF) or Glial Derived Neurotrophic Factor (GDNF), or other molecules may also regulate the relative levels of SNAP-25 isoforms (Hepp et al. 2001).

Different expression patterns between proteins of the same family have also been shown. Vamp-1 and -2, for example, are differentially expressed in the mature rat brain; while Vamp-2 is widely expressed and more abundant in most brain areas, Vamp-1 predominates in a few particular brain areas (Raptis et al. 2005). This could indicate that distinct family members could exert different functions, which is supported by the fact that Vamp-2 crucial activity in neuroexocytosis at early stages of brain development cannot be replaced by Vamp-1 (Schoch et al. 2001). Additionally, a wider range of Synaptotagmin

members is expressed in the first postnatal period (days 3–6) than in postnatal days 12–15 in neurons of rat models (Xiao et al. 2010). This different expression profile of Synaptotagmin proteins during development (higher vs. lower diversity) could indicate distinct roles of these proteins on neural development (Xiao et al. 2010).

SNARE proteins in glial cells

In addition to their role as supportive cells, glial cells can modulate neuronal activity levels, release chemical transmitters (gliotransmitters) and may also contribute to the maintenance of extracellular ion levels (Fellin 2009; Rossi and Volterra 2009). Gliotransmitters are able to activate neuronal receptors and consequently modify neuronal excitability and synaptic transmission (Rossi and Volterra 2009). Several SNARE proteins are expressed in astrocytes (Parpura et al. 1995; Zhang et al. 2004a), the most abundant glial cells in the central nervous system, and are essential to exocytosis of glutamate, D-Serine, BDNF and ATP; all of them stored in VAMP-2-containing vesicles (Araque et al. 2000; Zhang et al. 2004b; Mothet et al. 2005; Parpura et al. 2010; Parpura and Zorec 2010).

Apart from astrocytes, microglia are also important constituents of glia that play a role in neuron surveillance and maintenance in the brain (Hanisch and Kettenmann 2007; Graeber 2010). Moreover, there is evidence that they might be involved in synapse maturation and/or elimination (synapse pruning) (Graeber 2010; Paolicelli et al. 2011). SNARE proteins SNAP-25, SNAP-23, SytI and VAMP-2 are expressed in microglial cells (Hepp et al. 1999; Paolicelli et al. 2011). Myelin is formed by another type of glial cells in the central nervous system, the oligodendrocytes, and it is important to protect and increase the electrical impulses speed along the neuronal fiber (Sherman and Brophy 2005). Evidence of SNARE proteins expression in these glial cells suggests its involvement in the trafficking machinery that is essential in myelinating cells to allow temporal and spatial control by environmental cues (Feldmann et al. 2009; Baron and Hoekstra 2010).

SNARE complex and psychiatric disorders

The core SNARE complex proteins involved in neurotransmission are SNAP-25, VAMP (-1 or -2) and Syntaxin-1A. Cytoplasmic SNAP-25 forms a heterodimer with Syntaxin-1A, a plasma transmembrane protein, at the presynaptic terminal. Next, the vesicle transmembrane protein VAMP binds to this heterodimer forming the SNARE complex, joining plasmatic and vesicle membranes. An important regulatory protein to such membrane fusion event is Syt (I or II) that, upon calcium inflowing,

interacts with the SNARE complex, inducing fusion and allowing neurotransmitter release (Südhof 2013) (Fig. 1).

Due to its central role on neurotransmitter release, genes related to the SNARE complex and its regulatory proteins have been investigated in psychiatric disorders. Here, we review the overall findings regarding *SNAP25*, *VAMP1*, *VAMP2*, *STX1A*, *SYT1* and *SYT2* genes in relation to Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorders (ASD), Major Depressive Disorder, Bipolar Disorder and Schizophrenia susceptibilities, as well as animal model and expression studies. Given the aforementioned central role of SNARE complex on neurodevelopment, results for children and adult samples are presented separately whenever possible (summarized in Table 1) and distinct age-related effects are highlighted and discussed throughout the manuscript. Although genome-wide association studies have not yet implicated the reviewed genes on these disorders, several SNARE polymorphisms have been associated with such phenotypes in candidate gene studies, some of which being supported by meta-analytic studies (Supplementary Table S1).

Synaptosomal-associated protein 25 (*SNAP25*)

As mentioned above, the first evidence of a possible effect of SNAP-25 on abnormal neuropsychiatric development came from the *Coloboma* mouse, which was then considered an animal model for ADHD due to their hyperactive behavior. Based on this preliminary observation, the role of *SNAP25* gene variants (Chr.20p12.2) has been extensively investigated in relation to different psychiatric disorders (Table 1 and Supplementary Table S1). Studies on childhood ADHD have found multiple polymorphisms associated with the disorder (Feng et al. 2005; Kim et al. 2007; Guan et al. 2009; Zhang et al. 2011; Sarkar et al. 2012; Hawi et al. 2013) most of which, however, were not consistently replicated by independent studies (Sánchez-Mora et al. 2013; Gao et al. 2015).

Evidence implicating a functional role of some *SNAP25* variants may give additional support to these association findings. This is the case of rs362990 and rs6108461 SNPs, associated with childhood ADHD and for which a genotype-dependent *SNAP25* mRNA expression profile was observed (Hawi et al. 2013). The study reported a dose-dependent effect, where the increased presence of ADHD implicated alleles (A-rs362990 and A-rs6108461) were associated with decreased *SNAP25* transcript levels in the brain (Hawi et al. 2013). For other SNPs, apart from their association with childhood ADHD, a broader effect on psychiatric phenotypes has been suggested. For example, it was demonstrated that rs3787283 was nominally associated with ADHD in children and with comorbid Major Depressive Disorder in the same sample, thus affecting the

clinical heterogeneity of childhood ADHD (Kim et al. 2007). Furthermore, a subsequent study found that the same SNP was also associated with Major Depressive Disorder itself in adults (Wang et al. 2015).

Moreover, there are two meta-analyses indicating a significant association between the rs3746544 SNP and childhood ADHD (Forero et al. 2009; Gizer et al. 2009), which was further replicated by a subsequent study (Sarkar et al. 2012). Although others have failed in retrieving such result (Hawi et al. 2013; Gálvez et al. 2014; Gao et al. 2015), among the multiple *SNAP25* associations reported, this is indubitably the most robust finding on childhood ADHD susceptibility and, as depicted by meta-analytic studies, the T-allele can be considered as a risk-allele for ADHD in children (Supplementary Table S1).

Contrasting with this finding and the overall multiple-SNP implications scenario of *SNAP25* on childhood ADHD and despite having several SNPs tested, there is an almost absolute lack of significant findings regarding ADHD in adults (Sánchez-Mora et al. 2013; Olgiati et al. 2014). Such distinct effects of *SNAP25* variation on children and adults might be related to its developmentally dependent pattern of expression as discussed on the *Distinct expression profiles among isoforms and family members* topic. In fact, the only association of a *SNAP25* SNP with ADHD in adults was found precisely with rs3746544 (Herken et al. 2014); however, the observed effects of these SNP alleles for adults were in the opposite direction of what was observed for children samples (G for adults, while T for children as risk-allele). Such effect of the G-allele on adulthood ADHD is consistent with findings reported for other psychiatric disorders in adults, where it was also implicated on the susceptibility to Schizophrenia in two meta-analyses (Dai et al. 2014; Wang et al. 2015) and to Major Depressive Disorder (Wang et al. 2015).

Other SNPs spanning the *SNAP25* gene have also been associated with Schizophrenia (Carroll et al. 2009; Lochman et al. 2013), as well as with a broader construct of Schizophrenia-related phenotypes (Fanous et al. 2010). Furthermore, evidence of SNAP-25 expression studies in *post-mortem* brain support its relationship with Schizophrenia. SNAP-25 expression was demonstrated to be increased in a segment of the frontal cortex (Brodmann's Area 9) (Thompson et al. 1998—not replicated in Scarr et al. 2006), cingulate cortex (Gabriel et al. 1997) and orbitofrontal cortex (Ramos-Miguel et al. 2014). On the other hand, expression was decreased in cerebellum (Mukaetova-Ladinska et al. 2002), olfactory bulb (Egbujo et al. 2015), hippocampus (Fatemi et al. 2001), and segments of the temporal cortex (Brodmann's Area 20) and anterior prefrontal cortex (Brodmann's Area 10) (Thompson et al. 1998—not replicated by Gray et al. 2010) of Schizophrenia patients compared to controls. Moreover,

Table 1 *SNAP25*, *VAMP1*, *VAMP2*, *STX1A*, *SYT1* and *SYT2* genes overall findings regarding the five major psychiatric disorders

	Attention deficit hyperactivity disorder (ADHD) children	Attention deficit hyperactivity disorder (ADHD) adults	Autism spectrum disorders (ASD)	Major depressive disorder	Bipolar disorder	Schizophrenia
<i>SNAP25</i>	(+) Mill et al. (2002)	(-) Sánchez-Mora et al. (2013)	(-) Guerini et al. (2011)	(+) Kim et al. (2007) (in children with ADHD)	(+) Etain et al. (2010)	(-) Tachikawa et al. (2001)
	(+) Mill et al. (2005)	(-) Olgiati et al. (2014)	(-) Braida et al. (2015)	(+) Wang et al. (2015)		(-) Kawashima et al. (2008)
	(+) Feng et al. (2005)	(+) Herken et al. (2014)				(+) Carroll et al. (2009)
	(-) Brookes et al. (2005)					(+) Fanous et al. (2010)
	(-) Brookes et al. (2006)					(+) Lochman et al. (2013)
	(+) Gizer et al. (2009)					(+) Dai et al. (2014)
	(n) Guan et al. (2009)					(+) Wang et al. (2015)
	(+) Forero et al. (2009)					
	(+) Zhang et al. (2011)					
	(+) Sarkar et al. (2012)					
	(-) Sánchez-Mora et al. (2013)					
	(+) Hawi et al. (2013)					
	(+) Gálvez et al. (2014)					
	(-) Gao et al. (2015)					
<i>VAMP1</i>	(-) Sánchez-Mora et al. (2013)	(-) Sánchez-Mora et al. (2013)				
<i>VAMP2</i>	(-) Brookes et al. (2005)	(-) Sánchez-Mora et al. (2013)			(-) Jamra et al. (2008)	(-) Kawashima et al. (2008)
	(-) Brookes et al. (2006)	(+) Kenar et al. (2014)				
	(-) Sánchez-Mora et al. (2013)	(-) Gao et al. (2015)				
<i>STX1A</i>	(-) Brookes et al. (2005)	(+) Sánchez-Mora et al. (2013)	(n) Nakamura et al. (2008)			(+) Wong et al. (2004)
	(-) Brookes et al. (2006)	(+) Kenar et al. (2014)	(+) Durdiaková et al. (2014)			(-) Kawashima et al. (2008)
	(-) Guan et al. (2009)	(n) Olgiati et al. (2014)	(n) Nakamura et al. (2011)			(+) Mulle et al. (2014)
	(-) Sánchez-Mora et al. (2013)		(n) Malenfant et al. (2012)			
	(n) Gao et al. (2015)		(+) Tordjman et al. (2013)			
			(+) Roberts et al. (2014)			
<i>SYT1</i>	(-) Brookes et al. (2005)	(n) Sánchez-Mora et al. (2013)	(+) Szatmari et al. (2007)			
	(-) Brookes et al. (2006)					
	(n) Lasky-Su et al. (2008)					
	(n) Guan et al. (2009)					
	(n) Sánchez-Mora et al. (2013)					
<i>SYT2</i>	(+) Sánchez-Mora et al. (2013)	(-) Sánchez-Mora et al. (2013)				

Positive associations (+) with at least one polymorphism evaluated; (n) for nominal associations; and negative results (-) when no polymorphism was found associated

Duric et al. (2013) showed that subjects with Major Depressive Disorder had reduced expression levels of SNAP-25 in the hippocampus. However, when antidepressant usage and cause of death were considered, the results did not remain significant, suggesting that the expression pattern could be related to these factors. The same study demonstrated that rats with chronic unpredictable stress (a rat model for depression) presented a trend for decreased levels of Snap-25 in hippocampus.

Furthermore, no association was found with any SNAP25 SNP tested with ASD (Guerini et al. 2011; Braida et al. 2015), although associations with hyperactivity (Guerini et al. 2011) and with cognitive function (Braida et al. 2015) within ASD samples have been reported; and only one study assessed the role of SNAP25 variants on Bipolar Disorder (Etain et al. 2010). This later study found an association of rs6039769 with early-onset Bipolar Disorder; this same SNP was tested for childhood and adulthood ADHD and Schizophrenia with no significant results (Renner et al. 2008; Carroll et al. 2009; Sánchez-Mora et al. 2013) (Supplementary Table S1).

Apart from psychiatric disorder diagnoses, neurocognitive measures were also evaluated regarding SNAP25 genotypes. The rs363039 SNP was associated with working memory in childhood ADHD samples (Gao et al. 2015), and also in samples of healthy children and adults (Söderqvist et al. 2010). This SNP, along with other SNAP25 polymorphisms, was also associated with intelligence quotient (IQ) (Gosso et al. 2006, 2008) but with none of the psychiatric disorders reviewed here (Supplementary Table S1). Thus, it could be suggested that this SNP might influence neurocognitive measures across psychiatric and cognitive phenotypes.

It is noteworthy that most SNPs associated with a wide array of psychiatric disorders are located on the same genetic region, the 3' end of the gene, that was shown to be implicated in miRNA binding and expression control (Németh et al. 2013). It has been demonstrated that the T–T haplotype for rs3746544-rs1051312 forms a perfect binding site for miR-641, which increases mRNA degradation regulating SNAP-25 expression (Németh et al. 2013). Such T–T haplotype was previously associated with ADHD in children (Mill et al. 2004). Taking into account the known SNAP-25 role on axonal growth and synaptic plasticity, it seems plausible that lower SNAP-25 expression caused by the T–T haplotype might be related to ADHD susceptibility during childhood, a developmental stage where such neuronal processes are remarkably important. Interestingly, the same effect was not observed in adults; in fact, as noted above, the opposite rs3746544 allele (G) seems to confer risk to psychiatric disorders during adulthood, as it has been implicated in ADHD (Herken et al. 2014), Major Depressive Disorder (Wang et al. 2015) and Schizophrenia (Wang et al. 2015) in adults.

Altogether, SNAP25 findings show an interesting pleiotropic scenario pinpointing variants associated to the susceptibility to several psychiatric disorders at distinct developmental stages and suggest that fine control of SNAP-25 expression plays a central role on normal development.

Vesicle-associated membrane protein (*VAMP1* and *VAMP2*)

VAMP-1 is involved in neurotransmitter exocytosis at the presynaptic terminal (Bourassa et al. 2012). The association of *VAMP1* gene (Chr.12p13.31) polymorphisms has been tested in regards to ADHD susceptibility, both in children and adults (Sánchez-Mora et al. 2013); however, none of the tested SNPs showed significant effects (Table 1). Expression studies in *post-mortem* brains, on the other hand, have indicated that *VAMP1* mRNA levels are increased on the temporal lobe of Schizophrenia patients when compared to controls (Sokolov et al. 2000), and mRNA levels of a *VAMP1* orthologue in rats (*Vamp1*) were decreased in hippocampus of animal models of depression (Müller et al. 2011).

VAMP2 gene is located at Chr.17p13.1 region and is highly similar to *VAMP1* (McNew et al. 2000). The relationship between *VAMP2* and psychiatric disorders and related animal model phenotypes has been the focus of several studies. Regarding ADHD in children, several *VAMP2* SNPs were evaluated but none of them revealed any association (Brookes et al. 2005, 2006; Sánchez-Mora et al. 2013; Table 1). There was, however, a nominal association between one of these polymorphisms (rs1150) with visual working memory in a sample of children with ADHD, in which homozygotes for the minor allele (A) had better performance scores (Gao et al. 2015). On the other hand, only two variants have been investigated in respect to ADHD in adult samples; while Sánchez-Mora et al. (2013) did not observe association with the single *VAMP2* SNP addressed (rs8067606), Kenar et al. (2014) described a significant association with the 26 bp insertion/deletion (26pb Ins/Del) polymorphism of *VAMP2*. The 26pb Ins/Del is located at 2 kb from 3' region of *VAMP2*, in an intergenic region (Falbo et al. 2002), and the Ins-allele was significantly more frequent in adults with ADHD (Kenar et al. 2014) (Table 1 and Supplementary Table S1). Studies regarding other psychiatric disorders did not retrieve significant associations, such as for Schizophrenia (Kawashima et al. 2008) or Bipolar Disorder (Jamra et al. 2008). However, similarly to what was observed for *VAMP1*, increased *VAMP2* mRNA levels on the temporal lobe of Schizophrenia patients were found when compared to controls (Sokolov et al. 2000).

Mice models of depression induced by different types of stress (endogenous stress or unpredictable chronic stress)

showed reduced *Vamp2* mRNA levels in hippocampus (Malki et al. 2014) and *Vamp2* mRNA and protein levels in adrenal medulla (Santana et al. 2015). In rats, however, chronic restraint stress induced an increase of *Vamp2* mRNA levels in prefrontal cortex and in hippocampus, as well as increased protein levels in prefrontal cortex (Müller et al. 2011). In hippocampus, while Gao et al. (2006) also reported an increase in Vamp-2 protein levels, Müller et al. (2011) observed decreased Vamp-2. Such controversial findings between *Vamp2* mRNA (increased) and Vamp-2 protein levels (decreased) in rat hippocampus reported by Müller et al. (2011) might be due to possible post-transcriptional regulation of Vamp-2, as suggested by the authors. However, more studies are necessary to elucidate the opposite findings for Vamp-2 protein levels between Gao et al. (2006) and Müller et al. (2011) studies. Elfving et al. (2008) assessing a model of electroconvulsive therapy, a known treatment for depression, in rats observed an upregulation of *Vamp2* in hippocampus after seizures. Additionally, human studies with *post-mortem* brain tissue of patients with Major Depressive Disorder revealed that *VAMP2* mRNA levels were decreased in the prefrontal cortex compared to controls (Malki et al. 2014).

Syntaxin-1A (*STX1A*)

STX1A (Chr.7q11.23) polymorphisms have been investigated in relation to ADHD susceptibility in both children and adult samples. It is noteworthy that, although there are more studies with children, most associations were found with adult samples of ADHD. Of the five childhood ADHD studies, only one of them found a significant result (Table 1). The single associated *STX1A* SNP (rs875342) was found by Gao et al. (2015) comparing Chinese children with and without ADHD.

Regarding adults, the three studies that investigated the relationship between *STX1A* and ADHD have found significant associations (Sánchez-Mora et al. 2013; Kenar et al. 2014; Olgiati et al. 2014); nevertheless the implicated SNPs were not always the same across studies. Sánchez-Mora et al. (2013) have evaluated several SNPs, both in children and adult samples, and found four *STX1A* SNPs associated with ADHD during adulthood (Supplementary Table S1). The association of rs2228607 to ADHD observed in adults (Sánchez-Mora et al. 2013) was also found in an independent sample of adults, but in the opposite direction (Olgiati et al. 2014). These results are especially interesting since this polymorphism has been shown to be functionally relevant, where the G-allele is able to affect the mRNA splicing process, favoring the inclusion of intron 3 and resulting in decreased mRNA stability by enhancing nonsense-mediated mRNA decay (von Känel et al. 2013). A third study has implicated a

different *STX1A* SNP (rs35459363) on adult susceptibility to ADHD (Kenar et al. 2014). A possible implication of this SNP in psychiatric disorders during adulthood has also been suggested by a Schizophrenia susceptibility study in a sample from Canada and Portugal (Wong et al. 2004); however, this was not replicated in a Japanese sample (Kawashima et al. 2008) (Supplementary Table S1). Childhood ADHD studies have not directly investigated the effect of this SNP; nevertheless, no association was observed when its effect was assessed in ASD, which is another childhood onset psychiatric disorder (Nakamura et al. 2008).

High functioning autism was nominally associated to the functional *STX1A* rs2228607 SNP and rs4717806 in children in a Caucasian sample (Nakamura et al. 2008) and to rs6951030 in a Japanese sample (Nakamura et al. 2011). Asperger's Syndrome was associated to rs4717806 and rs941298 in adults (Durdiaková et al. 2014) (Table 1 and Supplementary Table S1). Moreover, the rs1569061 T-allele was over-transmitted to ASD probands, but other SNPs were not associated (Malenfant et al. 2012). Furthermore, copy number variations encompassing Chr.7q11.23 region have been associated with intellectual and developmental disabilities (Kaminsky et al. 2011), Schizophrenia (Mulle et al. 2014) and ASD (Malenfant et al. 2012; Tordjman et al. 2013; Roberts et al. 2014).

Animals submitted to unpredictable stress to induce depressive-like behavior presented lower *Stx1A* mRNA levels in the adrenal medulla when compared to controls (Santana et al. 2015). Concerning other expression studies, a lower *STX1A* mRNA expression was found in *post-mortem* brain tissues of adults with ASD, specifically in the anterior cingulate gyrus (Nakamura et al. 2011). Nevertheless, Schizophrenia patients present higher Syntaxin-1A levels in cingulate cortex (Gabriel et al. 1997; Honer et al. 1997) and in dorsolateral prefrontal cortex (Gil-Pisa et al. 2012—not found by Gray et al. 2010). Additionally, changes in the protein levels were not found in parietal cortex (Gabriel et al. 1997; Gray et al. 2010), frontal cortex (Gabriel et al. 1997) and prefrontal cortex (Gray et al. 2010). Moreover, in Schizophrenia patients a negative correlation between age and *STX1A* mRNA levels was demonstrated in the temporal cortex (Sokolov et al. 2000). Regarding Bipolar Disorder, an expression study did not find significant differences in the Syntaxin-1A levels between patients and controls in prefrontal cortex, dorsolateral prefrontal cortex and parietal cortex (Gray et al. 2010).

Synaptotagmin (*SYT1* and *SYT2*)

The SytI protein, encoded by the *SYT1* gene (Chr.12q21.2), acts as a Ca²⁺ sensor in vesicular trafficking and neurotransmitter release (Fernández-Chacón et al. 2001).

Although earlier childhood ADHD studies did not find any association (Brookes et al. 2005, 2006), subsequent studies found several *SYT1* SNPs nominally associated with the disorder (Guan et al. 2009; Sánchez-Mora et al. 2013) as well as with age of ADHD onset (Lasky-Su et al. 2008) (Supplementary Table S1). For adulthood ADHD, only one study has been conducted so far. Sánchez-Mora et al. (2013) found a nominal association between *SYT1* rs2251214 and ADHD in adults, but not in children. None of the other SNPs tested was associated with ADHD in adults (Sánchez-Mora et al. 2013). In addition, copy number variations were evaluated for ASD where several chromosomal regions were implicated, including a segment encompassing the *SYT1* gene (Szatmari et al. 2007).

Analyses of *SYT1* mRNA levels in post-mortem brains of elderly Schizophrenia patients and controls showed that there was an increased expression in the left superior temporal gyrus of the patients (Sokolov et al. 2000). Moreover, rats with depressive-like symptoms present an increase in *Syt1* mRNA levels in the hypothalamus (Ge et al. 2013). Despite that, rats that were submitted to models of electroconvulsive therapy did not show changes regarding *Syt1* mRNA expression levels in frontal cortex and hippocampus (Elfving et al. 2008). There was, however, a significant decrease in the paralogue *Syt3* mRNA levels in rat hippocampus after both single and repeated treatment exposure (Elfving et al. 2008).

SytII seems to play a role similar to *SytI* on the SNARE complex assembly (Nagy et al. 2006). *SYT2* SNPs (rs6427957-G and rs907697-T) were significantly associated with ADHD in children, but not in adults (Sánchez-Mora et al. 2013). The conflicting results between childhood and adulthood ADHD found for *SYT2* may indicate that some SNPs in genes related to neurotransmitter release might be age-specific factors, interfering on the age of onset or diagnosis persistence. More studies regarding this gene in other psychiatric disorders are needed to further elucidate its role on neurodevelopment.

SNARE genes and pharmacogenetics

The interindividual variability in treatment response to psychiatric drugs may be better understood through pharmacogenetic studies. Since the majority of the medications used to treat psychiatric disorders target components of the neurotransmitter systems, genes related to this pathway have earned attention and raised prominent results in psychiatric pharmacogenetics (Kitzmilller et al. 2011). In this context, genes encoding components of the SNARE complex and its regulatory proteins are candidates with potential effects on treatment response to psychiatric medications, since they play a key role in neurotransmitter release (Südhof 2013). Unfortunately, scarce

pharmacogenetic studies focusing on the components of this complex have been conducted so far.

Evidence from animal model studies evaluating SNARE complex mRNA or protein have supported the importance of this system in response to a variety of psychiatric drugs. Hess et al. (1996) evaluated the effects of the widely used psychostimulants in ADHD treatment, methylphenidate (MPH) and amphetamine, on locomotor activity using the *Coloboma* mice mentioned above compared to controls. Administration of amphetamine reduced the hyperactivity symptoms of *Coloboma* mice, but increased the locomotor activity of controls. On the other hand, MPH increased locomotor activity in both *Coloboma* and control mice, suggesting a more important role of *Snap25* on ADHD treatment with amphetamine than with MPH. Additionally, PC12 cells treated with MPH presented reduced *Syt1*, *Syt4* and *Stx1a* mRNA levels (Bartl et al. 2010). Thus, one could speculate that the SNARE complex may be involved in the response to commonly used ADHD medications.

There is also evidence of changes on SNARE proteins expression levels in different regions of the rat brain under antipsychotic treatment. More specifically, it has been shown that the use of typical antipsychotic drugs (chlorpromazine, haloperidol or trifluoperazine) alters *Snap-25* and Synaptophysin protein levels in a drug- and region-specific manner in the rat hippocampus (Barr et al. 2006). Moreover, Barakauskas et al. (2010) observed that treatment with haloperidol led to increased *Snap-25*, *Syntaxin* and *Vamp* protein levels in striatal regions of rats, whereas clozapine only increased levels of *Vamp* in the same region (Barakauskas et al. 2010). In the same sense, clozapine seems to downregulate *Stx1a* expression in frontal cortex whereas it upregulates expression in the parietal cortex (Sommer et al. 2010). Additionally, antidepressants have also been associated with changes in SNARE proteins expression levels. For example, Yamada et al. (2002) showed that chronic antidepressant treatment with imipramine and sertraline increased *Vamp-2* protein levels in the frontal cortex of rat, but reported no significant differences on *Snap-25* and *Stx1* protein levels. Taken together, these results from animal models suggest that components of SNARE complex may exert important functions on the treatment response to different psychiatric drugs and that genes encoding these components are considered good candidates for pharmacogenetic studies.

In clinical psychiatric studies, the most promising results regarding pharmacogenetics of SNARE complex genes are related to *SNAP25*. The rs3746544 polymorphism, in addition to their robust associations with childhood ADHD susceptibility (Forero et al. 2009; Gizer et al. 2009) was also investigated in studies evaluating the response to MPH in patients with ADHD. In preschoolers aged 3–5 years, the TT genotype of rs3746544 was

associated with better response to IR-MPH (immediate release MPH) when compared to G carriers. Additionally, this study also showed association between the G-allele and risk to irritability as treatment side effect (McGough et al. 2006). However, these results were not replicated in a subsequent study in patients with ADHD aged 6–17 years (McGough et al. 2009). More recently, this same SNP was associated with OROS-MPH (osmotic controlled release oral delivery system MPH) treatment response in a sample of children and adolescents aged 6–18 years, in which the TT and TG genotypes were associated with better therapeutic response (Song et al. 2014). These findings are in agreement with the results reported in preschoolers with IR-MPH (McGough et al. 2006). However, the single study that evaluated the role of this *SNAP25* SNP on MPH response in adults with ADHD did not retrieve any significant association (Contini et al. 2012). The rs3746544 polymorphism was also associated with efficacy of treatment and weight gain after 14 weeks of treatment in Schizophrenia patients with history of poor response to antipsychotics (Müller et al. 2005). Patients under treatment with clozapine, olanzapine, risperidone or haloperidol that carried the TT genotype showed a better clinical response, but also increased weight gain when compared to TG and GG genotypes. Such findings are in line with the results supported by two meta-analyses reporting the G-allele as risk to Schizophrenia susceptibility as described earlier (Dai et al. 2014; Wang et al. 2015). However, this SNP was not associated with treatment response in another study that evaluated patients with Schizophrenia being treated with quetiapine, risperidone, aripiprazole and olanzapine over a period of 8–12 weeks (Spellman et al. 2008).

Another well-studied *SNAP25* SNP, rs1051312, was also investigated in most studies mentioned above. This SNP was associated with IR-MPH treatment response and side effects in preschoolers with ADHD (3–5 years old), in which the T-allele was associated with worse treatment response and the C-allele predicted motor tics as a side effect (McGough et al. 2006). However, no association of this SNP with treatment response and side effects was found in a sample of children and adolescents (McGough et al. 2009). Regarding antipsychotics, this polymorphism was not significantly associated with clinical response or weight gain in patients with Schizophrenia (Müller et al. 2005; Spellman et al. 2008). Apart from *SNAP25*, other SNARE components are still poorly investigated in clinical pharmacogenetic studies. In one of the few studies, *VAMP2* gene polymorphisms were investigated on clinical response to the antidepressant fluvoxamine in a Japanese sample of adults with Major Depressive Disorder, but no significant association was found (Saito et al. 2007).

Given the relative scarcity of clinical pharmacogenetic studies, expression experiments may raise interesting possibilities for further investigations. An interesting example comes from the *post-mortem* analysis of protein expression levels in the prefrontal cortex of subjects with and without Schizophrenia, treated or not with antipsychotics. It was demonstrated that Syntaxin-1A protein levels were increased in Schizophrenia, but showed a slightly reduction with antipsychotic treatment (Gil-Pisa et al. 2012). *SNAP25*, *VAMP*, *Syt*, *Munc18-1a* and *Synaptophysin* expression was not altered in the brain of Schizophrenia patients without treatment, while in patients treated with antipsychotics drugs only *VAMP* had reduced expression levels (Gil-Pisa et al. 2012).

Despite more replication studies being warranted, the evidence up to now involving animal model, expression and clinical studies suggests that SNARE complex genes are important candidates to be investigated on response to different psychiatric drugs, including antipsychotics, psychostimulants and antidepressants. Provided that the SNARE proteins have different expression patterns throughout life, it is worth mentioning the importance of considering age groups in such pharmacogenetics studies, at least regarding MPH response. Thus, elucidating genetic variants that influence the effectiveness of treatment or the incidence of adverse effects will allow to perform early pharmacological intervention and improve the patient's prognosis.

Conclusion

In this review we addressed the state-of-the-art of genetic association findings and biological evidence linking SNARE complex to developmental psychiatry. We revisited studies exploring the relationship between SNARE genes (*SNAP25*, *VAMP1*, *VAMP2*, *STX1A*, *SYT1* and *SYT2*) and several psychiatric disorders and their treatments. Although still inconclusive, genetic association findings on psychiatric disorders susceptibility depict a promising overall scenario, with variants exerting distinct effects in children and in adults. Additionally, despite SNARE proteins usually being known by their role in neurotransmitter release, they participate in a wide variety of processes throughout life stages and are essential to neuropsychiatric development.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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